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THE EFFECT OF BREATHING 100 PER CENT OXYGEN IN PULMONARY EMPHYSEMA: CORRELATION OF CLINICAL IMPROVEMENT WITH CHANGES IN PULMONARY VENTILATION

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A DECREASE in pulmonary ventilation as a result of inhaling oxygen was first reported by Beddard and Pembrey[1] in a patient with pulmonary congestion due to heart failure. Campbell and Poulton[2] later noted a similar response in patients with primary chronic pulmonary disease, and also reported a concomitant increase in the carbon dioxide concentration of the expired air. In studies on the use of oxygen in cardiac insufficiency and chronic respiratory disease, the rise in arterial carbon dioxide tension was shown to be related to the decrease in pulmonary ventilation which results from the inhalation of an oxygen-enriched atmosphere.[3,4]

Barach[5] in 1938 observed an immediate change in the minute ventilation when 100 per cent oxygen was substituted for atmospheric air in patients with

pulmonary emphysema. He suggested this as a test for respiratory function, and emphasized that the value of the test was frequently enhanced when bronchospasm was previously relieved by the inhalation of 1.0 c.c. of 1 per cent epinephrine and 3.0 c.c. of 1 per cent Neo-Synephrine. A significant reduction in the pulmonary ventilation was produced by inhalation of 100 per cent oxygen in four of the eight patients tested and was followed ninety seconds later by chemical changes in the blood, that is, a rise in the oxygen saturation and carbon dioxide content of arterial blood. These findings were confirmed by studies reported by Bickerman and Beck,[6] who also suggested that the comparative ventilatory response to inhalation of oxygen and air could be used as a test of respiratory function in patients with chronic pulmonary emphysema.

The present investigation was intended to define more clearly this relatively simple measure of pulmonary function by presenting additional data on the minute volume of ventilation during the inhalation of air and 100 per cent oxygen in normal subjects as compared to patients with pulmonary emphysema and bronchial asthma. In addition, the effect of diaphragmatic breathing in patients with pulmonary emphysema was measured by determining the altered ventilatory response to breathing 100 per cent oxygen and correlated with clinical improvement following long-term therapy.

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METHODS

A total of 141 patients with well-documented chronic, nontuberculous pulmonary disease were selected as the subjects for this study. The majority, consisting of 121 patients, had pulmonary emphysema varying in severity from mild exertional dyspnea to severe shortness of breath at bed rest associated with cyanosis. The remaining twenty patients had uncomplicated bronchial asthma. A group of twenty-nine individuals with no evidence of pulmonary or cardiac disease were recruited among the staff members and patients in a hospital for chronic disease* to serve as healthy and diseased control subjects. The sex distribution and mean age of the groups studied are illustrated in Table I.

TABLE I. AGE AND SEX DISTRIBUTION OF 141 PATIENTS WITH CHRONIC PULMONARY DISEASE AND 29 NORMAL* SUBJECTS

DIAGNOSIS	NO. OF CASES	SEX		AGE (YR.)	
		MALE	FEMALE	MEAN	RANGE
Pulmonary emphysema	121	104	17	58.4	31–78
Bronchial asthma	20	14	6	45.0	16–68
Normal subjects*	29	23	6	36.1	21–62

*Twenty-one healthy individuals and 8 patients without pulmonary or cardiac disease.

*Goldwater Memorial Hospital, Columbia Research Division, New York.

Resting pulmonary ventilations were obtained with a Benedict-Roth spirometer. A motor blower on the inspiratory side served to overcome the slight resistance of the soda lime and one-inch tubing. Straight-line graphic tracings of the pulmonary ventilation while the subject was breathing air or 100 per cent oxygen were obtained by continuously replacing the oxygen consumed by the subject and removed from the bell by a modification of the method described by Eckman and Barach.[7] Oxygen was supplied from a reservoir spirometer to a ventilometer equipped with a Reichert counter so that simultaneous tracings of the minute ventilation and oxygen consumption could be recorded. By this method, the oxygen content of the bell while the subject was breathing room air remained relatively constant (20.8 per cent ± 0.5) without artificial disturbance of the patient's pulmonary ventilation.

The minute pulmonary ventilation breathing air or 100 per cent oxygen was recorded over a seven-minute period with the subject seated. Studies were not performed in the basal state, but each patient was required to rest for a period of thirty minutes before tracings were taken. An additional rest period of twenty to thirty minutes was allowed between tests to avoid the effects of fatigue and to permit the alveolar gases to equilibrate with room air. The minute ventilation determinations were performed in random fashion with approximately one-half the individuals breathing room air, followed by oxygen and a repeat study on air, while the remainder were first subjected to 100 per cent oxygen, thence to room air. . . .

In addition to the recording of the minute ventilation in the sitting position, fifty subjects in the combined patient and normal series were retested in the Trendelenburg position with the thorax tilted to an angle of fifteen degrees below the horizontal. Each patient in the emphysema group was evaluated clinically with respect to the degree of dyspnea prior to recording of the pulmonary ventilations. An arbitrary scale of I to IV was used to designate the degree of dyspnea, Grade I representing mild shortness of breath during customary activity; Grade II, moderate shortness of breath; Grade III, severe shortness of breath during slight exertion; and Grade IV, severe pulmonary insufficiency while at bed rest. Thirty-three patients were retested in two to six months following a course of therapy employing bronchodilator drugs, aerosols, and a training program designed to promote viscerodiaphragmatic breathing.

RESULTS

All the patients with pulmonary emphysema (121) manifested a decrease in the minute pulmonary ventilation when 100 per cent oxygen was substituted for room air. A positive correlation between the extent of the dyspnea as observed clinically and the fall in the minute pulmonary ventilation while the subject was breathing oxygen expressed as the per cent change from the ventilation on room air is illustrated in Table II. The patients with bronchial asthma showed a mean decrease of minus 2.6 per cent in the minute ventilation when room air was replaced by oxygen. Although no comparison could be drawn between the degree of bronchospasm present and the effect of breathing oxygen on pulmo-

nary ventilation, a variable degree of functional overdistention of the alveoli was suspected in the majority of the asthma patients. The normal subjects showed more variability in their response to a change from room air to 100 per cent oxygen than the patients with pulmonary disease. A slight but insignificant increase in the mean minute ventilation occurred when oxygen was inhaled. The mean per cent change of the individual differences was plus 1.4 per cent. The mean minute ventilations breathing air and oxygen for the patients and the normal subjects are represented graphically in Fig. 1.

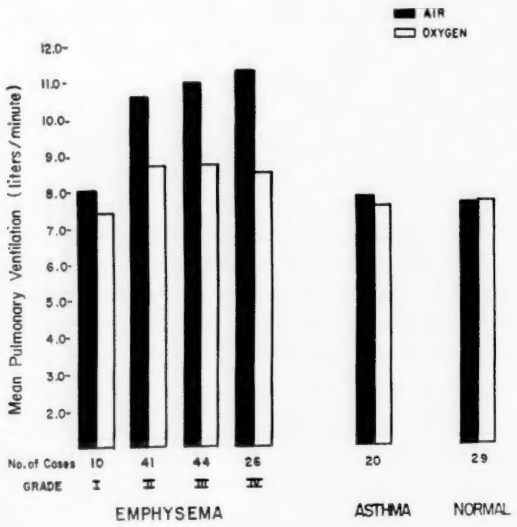

Fig. 1.—Comparison of the minute ventilation breathing air and 100 per cent oxygen in pulmonary emphysema and bronchial asthma patients and normal subjects.

The reduction in the pulmonary ventilation when 100 per cent oxygen is substituted for room air indicates a correlation with the clinical severity of pulmonary emphysema. No significant changes are demonstrated in the asthma and normal groups.

Following the recording of the pulmonary ventilation with air and oxygen, twenty-two patients with emphysema, eight with bronchial asthma, and twenty normal subjects were retested after lying in the head-down position. The individuals were placed on a board inclined fifteen degrees from the horizontal with a small pillow set beneath the head for comfort. They were rested in this manner for thirty minutes with the thorax tilted below the level of the abdomen. The pulmonary ventilation breathing air was diminished in all three groups, with the emphysema patients exhibiting the greatest fall, minus 17.5 per cent as compared with minus 7.5 per cent for the patients with asthma and minus 3.4 per cent in the normal subjects. As noted previously in patients with pulmonary emphysema,[8] the decrease in minute ventilation in the head-down position exceeded the change in ventilation when oxygen was substituted for air in the sitting position. The data are presented in Table III.

No significant change was evident in the oxygen consumption of patients breathing air and 100 per cent oxygen or those breathing air in the sitting and

head-down positions, either in the emphysema or normal group; however, further observations are indicated on oxygen consumptions of the emphysema group. The oxygen consumption in the asthma patients decreased 8 per cent when

TABLE II. THE MEAN PULMONARY VENTILATIONS BREATHING AIR AND 100 PER CENT OXYGEN IN PERSONS WITH PULMONARY EMPHYSEMA AND BRONCHIAL ASTHMA AND NORMAL SUBJECTS

DIAGNOSIS	GRADE	NO. OF CASES	PULMONARY VENTILATIONS (LITERS/MINUTE)*						PER CENT CHANGE
			AIR			OXYGEN			
			MEAN	RANGE	S.D.†	MEAN	RANGE	S.D.†	
Pulmonary emphysema	I	10	8.09	6.36–9.95	1.09	7.47	5.76–9.00	1.06	− 8.1
	II	41	10.69	5.65–16.8	4.05	8.73	4.90–15.1	2.16	−18.3
	III	44	11.08	5.95–16.7	2.59	8.74	5.16–15.0	2.18	−20.8
	IV	26	11.41	4.97–23.9	3.78	8.59	3.88–15.2	2.31	−23.2
Bronchial asthma		20	7.80	4.32–11.6	2.05	7.61	4.04–11.6	2.20	− 2.6
Normal subjects		29	7.72	4.33–11.2	1.55	7.78	4.35–11.3	1.52	+1 .4

*Body temperature ambient pressure, saturated.
†Standard deviation.

TABLE III. THE EFFECT OF THE HEAD-DOWN POSITION ON PULMONARY VENTILATION, OXYGEN CONSUMPTION, AND VENTILATORY EQUIVALENT AS COMPARED WITH THE CHANGES RESULTING FROM AIR TO OXYGEN BREATHING IN THE SITTING POSITION

DIAGNOSIS	NO. OF CASES	SITTING (MEAN VALUES)			HEAD DOWN 15° (MEAN VALUES)	
		AIR	OXYGEN	PER CENT CHANGE	AIR	PER CENT CHANGE FROM SITTING
Pulmonary Ventilation (L./min.)						
Pulmonary emphysema	22	10.1	8.8	−12.3	8.2	−17.5
Bronchial asthma	8	9.1	8.9	− 3.0	8.6	− 7.5
Normal subjects	20	7.4	7.6	+ 2.1	7.2	− 3.4
Oxygen Consumption (c.c./min./M.²)						
Pulmonary emphysema	22	174	176	+ 3.6	183	+ 7.2
Bronchial asthma	8	185	172	− 8.0	166	−11.3
Normal subjects	20	158	152	− 3.5	159	+ 1.6
Ventilatory Equivalent (c.c. O_2 cons./L. of P.V.)						
Pulmonary emphysema	22	31.6	36.6	+17.1	36.1	+16.6
Bronchial asthma	8	37.4	36.1	− 5.5	40.8	+ 0.9
Normal subjects	20	39.1	37.4	− 3.0	41.0	+ 5.2

TABLE IV. THE EFFECT OF LONG-TERM THERAPY, INCLUDING DIAPHRAGMATIC TRAINING, ON THE VENTILATORY RESPONSE TO AIR AND 100 PER CENT OXYGEN IN THIRTY-THREE PATIENTS WITH PULMONARY EMPHYSEMA

	PULMONARY VENTILATIONS (LITERS/MINUTE)						
	AIR			OXYGEN			PER CENT CHANGE
	MEAN	RANGE	S.D.*	MEAN	RANGE	S.D.*	
Before therapy	11.59	5.15–23.90	3.45	8.91	4.46–15.2	2.38	−22.1
After therapy	9.90	5.70–21.39	3.18	8.91	5.64–16.2	2.40	− 8.3

*Standard deviation.

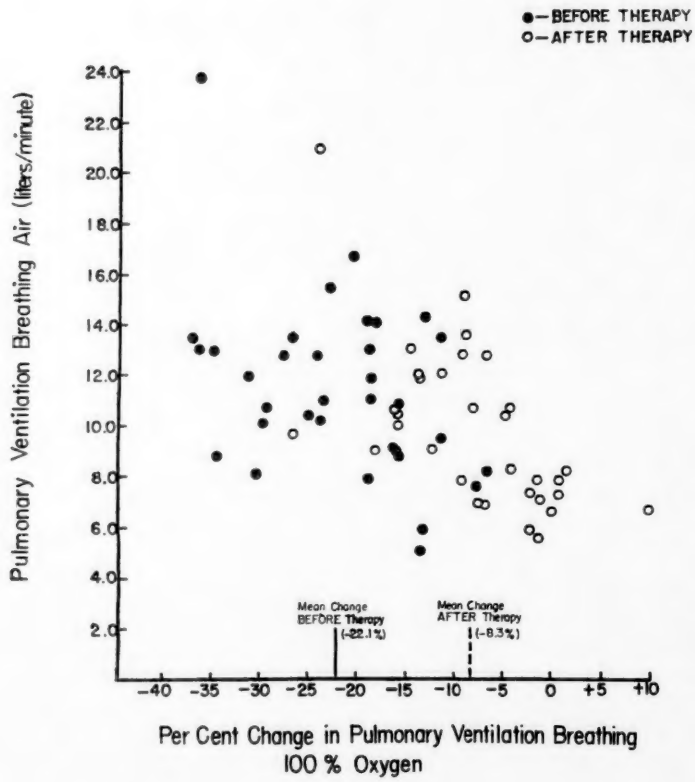

Fig. 2.—The effect of long-term diaphragmatic training on the change in the pulmonary ventilations of thirty-three emphysema patients breathing air and oxygen.

A marked lowering of the per cent change in pulmonary ventilation breathing 100 per cent oxygen as compared with air is illustrated following a two- to six-month therapeutic program.

oxygen was breathed and 11.3 per cent when air was breathed by subjects in the head-down position. This series was considered too small to indicate a significant trend.

The ventilatory equivalent (V. E.), expressed as milliliters of oxygen consumed per liter of ventilation per square meter of body surface area, showed no consistent pattern in the normal and asthma groups. However, there was a mean increase in V. E. of 17 per cent in the emphysema patients when oxygen was substituted for room air and a similar increase when air was breathed in the head-down position (Table III).

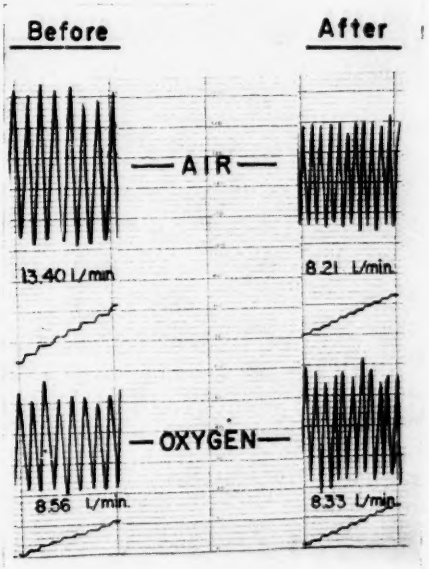

Fig. 3.—Spirometric tracing of pulmonary ventilation breathing air and 100 per cent oxygen in a patient with pulmonary emphysema before and after six months' therapy.

The spirographic tracings of a patient with Grade IV emphysema illustrating the marked reduction in resting minute ventilation and in the air-oxygen difference after six months of therapy, including bronchodilator aerosol, aminophylline, and diaphragmatic exercises.

It was of interest to compare the ventilatory studies in thirty-three patients with severe pulmonary emphysema (Grades III and IV) following a course of long-term therapy. In the initial tests, a mean decrease of 22.1 per cent in the minute ventilation was recorded when oxygen replaced room air. Following treatment, including among other measures training in diaphragmatic breathing,[9-11] the mean decrease was only 8.3 per cent, which corresponded to the mean decreases found in the group with Grade I emphysema. This is illustrated in Table IV and Fig. 2. In a patient with Grade IV emphysema, the initial minute ventilation fell from 13.40 L. to 8.56 L. when 100 per cent oxygen was inhaled. Following five inhalations of bronchodilator aerosol, manual compression of the diaphragm ten times, and the initiation of diaphragmatic movement as observed under fluroscopy, a retest that same day showed a minute ventilation on air of 7.95 L. and 7.48 L. while breathing oxygen. After six months of therapy as

described later, there was no significant difference in the pulmonary ventilation between air and oxygen: 8.21 L. with air and 8.33 L. with oxygen (Fig. 3).

DISCUSSION

In previous reports by Dripps and Comroe[12] and Otis and his associates,[13] the inhalation of 100 per cent oxygen resulted in a slight initial depression of the minute respiration of normal subjects which was followed by a mild increase in ventilation averaging 7 per cent after eight minutes. In the present series, the normal individuals tested over a seven-minute period had a slight but insignificant increase in minute ventilation while breathing oxygen.

The thirty-three patients with severe pulmonary emphysema who were studied before and after long-term therapy carried out a daily program designed to alleviate bronchospasm and improve diaphragmatic breathing.[10,14] The majority of the patients were hospitalized for a ten- to fourteen-day period, during which the following program was instituted:

1. Measures designed to relieve bronchospasm included the inhalation of aerosols consisting of either 2.25 per cent racemic epinephrine (Vaponefrin*), 0.5 per cent isopropyl arterenol (Isuprel†), or 2.5 per cent racemic epinephrine with 0.5 per cent atropine sulfate (Dylephrin‡) on arising, at 4 P.M., and on retiring. Oral medication consisting of 0.2 Gm. aminophylline or combinations of 0.2 Gm. aminophylline and 0.016 Gm. ephedrine (Dainite§) was ingested in the fasting state before breakfast and on going to bed. Where the sputum appeared tenacious and difficult to expectorate, 1.0 c.c. of a saturated solution of potassium iodide was given after each meal, or 0.5 c.c. four times a day.

2. Training in diaphragmatic breathing included the following procedures: (a) Manual elevation of the diaphragm following the inhalation of the bronchodilator aerosol by compression of the upper abdomen and lower rib cage with the palms of the hands was performed by the patient ten times during the expiratory phase of respiration. (b) Viscerodiaphragmatic breathing was encouraged by having the patient recline in the head-down position for one hour three or four times daily. The placing of a sandbag weighing 12 pounds over the lower abdomen frequently resulted in greater diaphragmatic mobility with cessation of upper costal movement. When diaphragmatic breathing was mastered in the recumbent position, as evidenced by protrusion of the abdomen with little or no chest movement during inspiration, the same exercise was practiced while sitting and walking. Diaphragmatic breathing was aided in the upright position by applying a Gordon-Barach belt# over the lower abdomen.

3. In the presence of severe pulmonary insufficiency accompanied by hypoxia and dyspnea at rest, a program of oxygen inhalation employing a double-bent nasal catheter was first instituted. Beginning with 1 or 2 L. of oxygen per

*Supplied by the Vaponefrin Co., Upper Darby, Pennsylvania.
†Supplied by Winthrop-Stearns, Inc., New York.
‡Supplied by Irwin Neisler, Decatur, Illinois.
§Supplied by Irwin Neisler, Decatur, Illinois.
#Made by Spencer Co., New Haven, Connecticut.

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minute, the flow rate was increased 1 L. per minute each day to 7 L. per minute and then gradually lowered again after a period of ten days. Toward the end of this period, walking was performed while the subject inhaled 8 to 10 L. per minute of oxygen through a double-bent nasal catheter attached to extension tubing. As exercise tolerance increased, the number of steps taken were increased, and continuous oxygen was discontinued.

Following discharge from the hospital, these patients continued their treatment at home with follow-up in the clinic or office. Pulmonary ventilations on both air and oxygen were repeated two to six months after instituting the training program.

A relatively simple test which may be employed clinically to aid in differentiating pulmonary emphysema from certain chronic diseases of the respiratory system is suggested by the fall in the resting pulmonary ventilation when 100 per cent oxygen is substituted for air. In addition, there appears to be a positive correlation between the extent of this decrease in minute ventilation and the severity of the emphysematous process. Four patients in this series with severe pulmonary emphysema, on whom blood gas analyses were performed, showed a similar positive correlation between the decrease in pulmonary ventilation breathing oxygen and the degree of arterial oxygen unsaturation. Barach[5] also reported corresponding changes in pulmonary ventilation when oxygen-enriched mixtures were breathed, and related them to the arterial oxygen saturation. The elimination of the anoxic stimulus to respiration when 100 per cent oxygen is inhaled appeared to be of greater importance in the regulation of minute ventilation than the increase in blood pCO_2 or the lowering of the blood pH in these patients with pulmonary emphysema.

Improvement in diaphragmatic breathing with more efficient ventilation of the lung bases such as occurred in the head-down position or after long-term training in viscerodiaphragmatic breathing results in a lowered resting ventilation with a reduction in the air-oxygen difference. Thirty-three patients with severe incapacitating pulmonary emphysema who were significantly improved following long-term therapy revealed graphically a comparable response in their air-oxygen ventilatory test.

It should be emphasized that none of the patients taking part in this study had clinical evidence of cardiac decompensation. Breathing an oxygen-enriched atmosphere was noted by Barach and Richards[3,4] to decrease the pulmonary ventilation of patients in congestive heart failure. Our observations on the effects of the head-down position in cardiac patients indicated a marked variation in response; a sharp rise in the minute ventilation was observed in most of these subjects who exhibited predominant left-sided failure; a small group with cor pulmonale revealed a fall in ventilation, similar to patients with uncomplicated pulmonary emphysema. One patient with left ventricular failure, pleural effusion, and pulmonary emphysema manifested a significant drop in ventilation and relief of dyspnea, even though fluid shifted from the right base to the right apex.

SUMMARY

The resting pulmonary ventilations breathing air and 100 per cent oxygen were recorded in 121 patients with chronic pulmonary emphysema, twenty patients with bronchial asthma, and twenty-nine control subjects of whom twenty-one were healthy individuals and eight were ambulatory patients who had no evidence of cardiac or pulmonary disease. A significant reduction in the minute ventilation was observed in pulmonary emphysema when oxygen was substituted for air, with the extent of this decrease indicating a positive although rough correlation with the clinical severity of the disease. Insignificant changes in pulmonary ventilation took place in the asthma patients and control subjects under identical testing conditions.

Lowering of the minute ventilation also occurred when patients with pulmonary emphysema were placed in the head-down position. The decrease in ventilation expressed as a per cent change from the sitting position was of the same order as the air-oxygen difference, and was probably due to the initiation of diaphragmatic breathing resulting in increased aeration of the lower lobes and more efficient alveolar ventilation.

Thirty-three patients with severe pulmonary emphysema were retested after two to six months of treatment designed to train and encourage viscero-diaphragmatic breathing and to ameliorate bronchospasm. The mean per cent change in ventilation between breathing air and oxygen fell from minus 22 to minus 8, and this was paralleled by the clinical improvement in exercise tolerance.

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REFERENCES

1. Beddard, A. P., and Pembrey, M. S.: Observations on Pulmonary Ventilation in Disease, Brit. M. J. **2**:580, 1908.
2. Campbell, J. M. H., and Poulton, E. P.: Effect on Breathless Subjects of Residence in Oxygen Chamber, Quart. J. Med. **20**:141, 1927.
3. Barach, A. L., and Richards, D. W.: Effects of Oxygen Therapy in Congestive Heart Failure, Arch. Int. Med. **48**:324, 1931.
4. Richards, D. W., and Barach, A. L.: Prolonged Residence in High Oxygen Atmospheres. Effects on Normal Individuals and on Patients With Chronic Cardiac and Pulmonary Insufficiency, Quart. J. Med. **27**:437, 1934.
5. Barach, A. L.: Physiological Methods in Diagnosis and Treatment of Asthma and Emphysema, Ann. Int. Med. **12**:454, 1938.
6. Bickerman, H. A., and Beck, G. J.: Physiologic Factors in the Treatment of Chronic Hypertrophic Pulmonary Emphysema, Ann. Int. Med. **36**:607, 1952.
7. Eckman, M., and Barach, A. L.: Horizontal Respiratory Graphs by Automatic Feed of Oxygen Into a Basal Metabolism Apparatus, Proc. Soc. Exper. Biol. & Med. **36**:138, 1937.
8. Barach, A. L., and Beck, G. J.: The Ventilatory Effects of the Head-Down Position in Pulmonary Emphysema, Am. J. Med. **16**:55, 1954.
9. Heckscher, H.: The Emphysema of the Lungs, Its Symptoms and Relations to Other Diseases, Acta med. scandinav. **120**:349, 1945.
10. Barach, A. L.: Remissions in Bronchial Asthma and Pulmonary Emphysema, J.A.M.A. **147**:730, 1951.
11. Barach, A. L.: Breathing Exercises and Allied Aids to Breathing in the Treatment of Pulmonary Emphysema, M. Rec. & Ann. **46**:323, 1952.
12. Dripps, R. D., and Comroe, J. H.: The Effect of the Inhalation of High and Low Oxygen Concentrations on Respiration, Pulse Rate, Ballistocardiogram, and Arterial Oxygen Saturation (Oximeter) of Normal Individuals, Am. J. Physiol. **149**:277, 1947.
13. Otis, A. B., Rahn, H., Brontman, M., Mullins, L. J., and Fenn, W. D.: Ballistocardiographic Study of Changes in Cardiac Output Due to Respiration, J. Clin. Invest. **25**:3, 1946.
14. Barach, A. L.: Advances in the Treatment of Diseases of the Chest, Cincinnati J. Med. **30**:131, 1949.

RELATION OF BLOOD PRESSURE LABILITY TO PROGNOSIS IN HYPERTENSIVE VASCULAR DISEASE

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THIRTY years ago the view was expressed that isolated blood pressure determinations in hypertensive patients were variable and their significance inconclusive. Levels at rest, however, were found to be related to the severity of the disorder.[1] Despite repeated similar observations there remains considerable divergence of opinion, both as to the association of the degree of elevation with complications and prognosis, and the conditions under which measurements should be made.[2] Much of the controversy stems from the fact that ambulatory blood pressure values are obtainable more readily than are basal values, and that correlations of both these levels with the entire evolution of the disease are investigated rarely.

It is hoped that the data to be presented, comparing "casual" and "resting" blood pressure values in hypertensive patients whose total disease history is known, will serve to clarify this problem further.

METHOD OF STUDY

Observations were made on fifty patients with documented hypertensive vascular disease, divided into two equal groups depending on the presence or absence of blood pressure lability. All were selected from a series of previously normotensive patients followed from the known time of onset of hypertension until death from a cause presumably related to their disease,[3] provided only that there was adequate information concerning "resting" as well as "casual" blood pressure values. Each patient was examined generally at yearly intervals and received no specific therapy.

For the purpose of the present study the blood pressure was regarded as *labile* when "resting" levels were more than 40/20 mm. of mercury below average "casual" levels, as *nonlabile* when "resting" levels were less than 30/15 mm. below average "casual" levels. "*Casual*" values refer to single blood pressure determinations secured in the sitting or standing position under quiet conditions

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TABLE I. HYPERTENSIVE VASCULAR DISEASE: COMPARISON BETWEEN PATIENTS WITH AND WITHOUT BLOOD PRESSURE LABILITY

NO.	SEX	WT. (LB.)	"CASUAL" B.P. RANGE	AV. "CASUAL" B.P. (MM. HG)	"RESTING" B.P.	AGE AT ONSET	AGE AT DEATH	DURATION H.V.D.* (YR.)	COMPLICATIONS				PRIMARY CAUSE OF DEATH
									CORONARY	CEREBRAL	RETINOPATHY	RENAL	
Labile group: "Resting" B.P. more than 40/20 mm. Hg below "casual" B.P.													
1	F	158	240/120–160/90	189/107	144/84	37	44	7	+	0	0	+	Cardiac
2	M	150	236/130–220/120	225/124	180/100	30	39	9	+	0	+	+	Renal
3	F	168	200/116–180/100	190/108	136/80	41	53	12	0	+	0	0	Cerebral
4	F	110	190/200–170/100	181/114	140/80	35	49	14	+	+	0	0	Cardiac
5	M	164	230/130–160/110	196/120	154/96	30	46	16	+	0	0	0	Cardiac
6	F	138	240/140–200/106	228/123	180/100	27	43	16	0	0	+	+	Not known
7	F	120	190/110–160/98	178/107	132/78	40	58	18	0	+	0	0	Cerebral
8	F	—	216/146–190/100	208/126	136/86	42	60	18	+	0	0	0	Cardiac
9	F	138	190/140–150/100	177/120	130/96	29	48	19	+	0	0	+	Renal
10	M	160	236/150–190/120	210/138	160/110	28	48	20	0	0	+	+	Renal
11	F	—	190/116–160/90	178/96	130/70	43	64	21	+	0	0	0	Not known
12	F	176	220/138–142/88	183/121	140/90	38	59	21	0	+	0	0	Not known
13	M	—	250/150–170/104	216/130	160/92	47	60	23	+	+	0	0	Cerebral
14	F	—	190/114–140/90	168/108	120/76	46	69	23	+	0	0	0	Not known
15	F	151	220/130–186/100	205/116	150/94	44	68	24	0	0	0	0	Not known
16	F	178	210/120–160/100	194/114	140/90	34	59	25	+	0	0	0	Cardiac
17	F	137	225/135–200/120	214/125	170/100	19	47	28	+	0	+	+	Renal
18	F	240	230/150–200/120	219/130	150/196	19	47	28	+	0	0	0	Cardiac
19	F	121	220/120–166/96	197/116	140/80	28	56	28	0	+	0	0	Cerebral
20	F	188	240/150–180/100	204/124	160/100	36	64	28	+	0	+	+	Cardiac
21	F	158	240/165–220/120	232/134	148/88	30	62	32	+	0	0	0	Not known
22	M	183	210/136–178/100	191/124	140/90	27	59	32	+	0	0	0	Cardiac
23	F	170	236/136–150/88	194/119	120/74	26	61	35	0	+	0	0	Cerebral
24	F	116	260/140–230/130	251/137	162/90	32	67	35	+	+	0	+	Cerebral
25	F	154	260/140–190/110	240/132	140/80	23	61	38	+	+	0	0	Cardiac
Av. or %	20%M	156	224/134–178/104	203/121	146/89	33	56	23	68%	36%	20%	32%	16% renal

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Nonlabile group: "Resting" B.P. less than 30/15 mm. Hg below "casual" B.P.

1	M	133	290/160–250/150	260/156	250/150	31	34	3	+	0	+	+	Renal
2	M	160	230/144–200/120	214/130	196/116	34	39	5	0	0	+	+	Renal
3	M	142	228/140–170/120	196/133	170/120	35	40	5	+	0	+	+	Cardiac
4	M	182	260/160–222/138	247/145	218/134	22	28	6	0	0	+	+	Renal
5	F	—	248/140–180/130	201/136	184/134	30	37	7	0	0	+	+	Not known
6	M	154	220/132–190/120	199/126	192/124	27	34	7	0	+	0	+	Cerebral
7	F	120	220/120–190/110	212/113	190/110	42	50	8	0	0	0	+	Renal
8	F	97	196/130–172/116	185/121	180/120	35	43	8	0	0	+	+	Renal
9	M	—	226/146–200/120	216/130	200/126	38	47	9	+	0	0	+	Cardiac
10	M	204	250/128–200/116	223/122	196/108	35	44	9	+	0	+	0	Cardiac
11	M	165	230/150–200/130	222/138	212/140	30	39	9	0	0	+	+	Renal
12	M	124	260/150–250/150	254/150	240/150	28	40	12	0	0	+	+	Renal
13	M	—	235/140–200/126	210/130	190/124	22	34	12	0	0	0	+	Renal
14	F	110	212/130–200/120	208/124	196/120	26	40	14	+	0	+	0	Cardiac
15	M	128	240/140–190/128	208/135	180/130	33	48	15	0	0	+	+	Renal
16	M	140	206/110–176/100	189/106	168/94	23	38	15	+	+	0	0	Cardiac
17	F	136	196/116–186/108	191/113	184/108	31	46	15	0	+	0	+	Cerebral
18	M	156	216/120–196/110	200/114	200/100	29	44	15	0	0	+	+	Renal
19	F	170	190/116–180/110	186/113	176/110	23	39	16	+	0	+	+	Cardiac
20	M	158	200/120–160/94	183/108	170/90	44	60	16	0	0	0	0	Not known
21	M	161	216/114–170/100	184/104	184/104	37	55	18	0	+	0	+	Cerebral
22	F	139	200/120–190/100	196/106	194/114	30	49	19	+	0	0	0	Cardiac
23	M	178	190/110–182/100	185/105	178/100	19	40	21	0	0	+	+	Renal
24	M	156	240/126–200/110	217/120	192/108	42	65	23	0	+	0	0	Cerebral
25	F	157	230/130–176/100	188/107	160/96	33	59	26	+	+	0	0	Not known
Av. or %	68%M	149	225/131–193/117	207/123	192/117	31	44	13	36%	24%	56%	72%	44% renal

*H.V.D. = hypertensive vascular disease.

in the office or clinic by a physician well known to the ambulatory patient. In each instance at least three and usually many more such readings were available, covering a period of not less than three years and taken within five years of the time of the patient's death. The range and average were obtained from these readings. "*Resting*" values were also determined within five years of the termination of the disease and refer to the lowest blood pressure recorded in the hospital in the early morning by a physician with the subject quiet and relaxed in bed. If any single such reading was more than 40/20 mm. of mercury below the previously obtained average "casual" level, no efforts were made to secure lower readings; if less than this amount, the lowest systolic and diastolic values after at least three weeks of hospital bed rest, or the lowest of five or more determinations taken at one-half-minute intervals and after not less than five days of bed rest, were termed the "resting" level. No data concerning lability or its absence were obtained from febrile patients, from those who had previously sustained a myocardial infarction or cerebral vascular accident, or from patients with pain, shock, uremia, obvious anxiety, or terminal disease at the time of the study.

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RESULTS

The results are summarized in Table I. They indicate that the "labile hypertensive" patients died at an average age of 56, twenty-three years after the known onset of an elevated blood pressure, in contrast to the "nonlabile" patients who died at an average age of 44, thirteen years after known onset. The age at onset in the two age groups was almost the same, whereas the total duration of hypertension in the two groups was significantly different—five times the standard error. In addition, the age at death of the nonlabile group was significantly earlier statistically than the mean age at death (52 ± 9.6 years) of the over-all series from which these patients were selected.[3]

Other differences existed between the two groups. Twenty per cent of the labile series were male, as compared to 68 per cent among the nonlabile subjects ($p = <0.01$). This sex difference does not account for the difference in age at death.[3] The average weight of the labile patients, recorded at about the time of the "resting" blood pressure determination, was slightly greater although not by a definitely significant margin.

The average maximum "casual" blood pressure of the two groups proved to be almost identical. As one might expect, however, the range of "casual" values was wider in the labile series; nevertheless, these greater fluctuations were insufficient to be reflected in the average. It is noteworthy that "resting" levels in the labile group, even after years of sustained disease in most instances, were frequently within normal limits. In the twenty-five patients exhibiting lability, rest and relaxation resulted in seven systolic blood pressure readings of less than 140 mm. of mercury and eleven diastolic readings of less than 90 mm.

As the hypertensive vascular disease evolved in the two groups, evidences of coronary artery disease (here defined as electrocardiographic signs of myocardial damage, angina pectoris, or myocardial infarction) and cerebral vascular accidents developed more frequently in the labile series, while retinopathy (hemor-

rhages, exudates, or papilledema) and renal damage (proteinuria clinically on a nephrosclerotic basis) were encountered more commonly in the nonlabile group. Except for the cerebral complications, these differences were significant ($p = < 0.03$). Four labile patients died of causes primarily related to progressive kidney damage and uremia, in comparison to eleven patients in the nonlabile group.

COMMENT

This study, relating the presence or absence of blood pressure lability to the natural history of hypertensive vascular disease, supports the concept that single and often multiple "casual" readings of the arterial tension are of little or no value prognostically. On the other hand, "resting" levels bear a definite statistical association with the total duration of life and the average age at death, a lack of lability pointing in general toward a less favorable course. As data were secured during the final five years of illness, it is possible that many of those with little fluctuation in blood pressure exhibited lability at an earlier stage; hence one should regard the presence of the nonlabile state as a more ominous prognostic sign rather than the presence of lability as a guarantee of continued good fortune.

From the present study it may be concluded that lability of blood pressure is more common in women, perhaps more common in obese individuals. Of note, however, is the fact that lability is not unusual even after many years of established disease and that its presence cannot be gauged necessarily by measurements of blood pressure as obtained casually.

It is apparent further that arteriosclerotic complications are more likely to occur in those who show fluctuations in the arterial tension and lower "resting" values, whereas arteriolosclerotic complications and the accelerated phase of the disease are more likely in those of the nonlabile type. This might be taken to indicate that intermittent decreases of blood pressure following rest or relaxation serve to protect the individual from arteriolar damage. Such a conclusion need not be drawn from the current data for it may be that arteriolar pathology, together with fixed levels of blood pressure, stems from a separate mechanism. The preponderance of arteriosclerotic complications in the labile hypertensive as compared with the stable hypertensive case series may be to a large extent related to the average age at death of 56 years in the former and 44 in the latter.

As a means of evaluating the course of hypertensive vascular disease, determinations of "resting" blood pressure would seem to be of greater significance than "casual" measurements. Interpretations of the effects of hypotensive drugs and the mechanisms through which possible benefits are obtained may be subject to error unless the presence or absence of blood pressure lability is taken into consideration.

SUMMARY

Utilizing "casual" versus "resting" blood pressure values, observations were made on fifty patients with documented hypertensive vascular disease whose total disease history was known. The duration of hypertension and the average age at death were significantly less in those with nonlabile blood pressure readings.

"Casual" values alone were of little or no prognostic significance. Lability of blood pressure was not unusual even after many years of established disease. Arteriosclerotic complications were more frequent in the labile series, whereas arteriolosclerotic changes were encountered more commonly in the nonlabile. Determinations of "resting" blood pressure are important in the evaluation of the hypertensive patient.

REFERENCES

1. Blankenhorn, M. A.: The Effect of Sleep on Normal and High Blood-Pressure, Tr. A. Am. Physicians **40**:87, 1925.
2. A Symposium on Essential Hypertension, Boston, 1951, The Commonwealth of Massachusetts.
3. Perera, G. A.: Hypertensive Vascular Disease; Description and Natural History, J. CHRON. Dis. **1**:33 (Jan.) 1955.

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UNTREATED SYPHILIS IN THE MALE NEGRO

Pathologic Findings in Syphilitic and Nonsyphilitic Patients

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THE energies and talents of many people and groups have been contributed in the planning and execution of this long-term study. It has involved a large group of individuals, physically distant from various of the individuals and organizations cooperating in the conduct of the operation. Numerous medical, social, administrative, and financial entities have been coordinated and timed to cover the life span of the study group.

In this paper, the autopsies were performed largely by Dr. J. J. Peters who thus takes the responsibility for the discussions and interpretations of the gross material. Dr. James H. Peers has reviewed personally all of the available tissue with respect to the cardiovascular system and has worked over the findings of his predecessors with respect to the reported microscopic interpretations; thus, he takes full responsibility for the discussion and interpretation of the histologic data.

The study was set up in a manner as to channel all of the autopsy material to the United States Public Health Service, Washington, D. C., for histologic examination. Throughout the years, with changing administrative structures, Dr. R. D. Lillie has been director of the various units working over the material, and has been charged with supervision of the work. Numerous pathology trainees under his supervision, over the years, have made the histologic studies

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Note: This article is one of a series on untreated syphilis in the male Negro which the Venereal Disease Program plans to assemble into a monograph. Single copies of the monograph will be made available upon request to the Venereal Disease Program, Division of Special Health Services, United States Public Health Service, Washington 25, D. C.

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on material as it was submitted, so that the summary, at this stage, rests upon the work of a large number of people whose individual contributions, unfortunately, cannot be identified by name.

Further acknowledgment for invaluable assistance must be given to the following:

The Milbank Memorial Fund, for provision of funds for payment of burial and autopsy expenses, without whose cooperation this study would have been impossible.

The Tuskegee Institute, Tuskegee, Alabama, for administration of the funds locally in payment of burial and autopsy expenses.

The Veterans Administration Hospital, Tuskegee, Alabama, for making available the voluntary services of Dr. J. J. Peters and x-ray and electrocardiogram facilities.

Dr. Murray J. Smith, Health Officer, Tuskegee, Alabama, for local supervision of the program since its inception.

Miss Eunice Rivers, Public Health nurse, whose devotion to the study and to the welfare of this group of patients over the twenty years has been in large part responsible for the opportunity to secure cooperation of the patient and family in permitting post-mortem study.

The various undertaking establishments at Tuskegee, Alabama, whose cooperation has been essential to the success of this phase of the work.

The members of the Division of Venereal Disease, Public Health Service, who in diverse capacities have had responsibility for continued direction of the study and for the gathering and processing of the data.

The serology laboratories, first of the Hygienic Laboratory, United States Public Health Service, and then of the Venereal Disease Research Laboratory for performance of the serologic testing procedures.

In all of these instances, the contributions of time, thought, and energy of many individuals with the full knowledge that the fruits of their efforts would not mature until years later, and in other hands, have been vital. As in all such lifetime studies the devotion of these scientists and public health workers to the search for knowledge for the sake of knowledge and with selflessness must here be acknowledged.

This report provides the first opportunity to correlate pathologic findings with clinical and serologic findings in a group of syphilitic and nonsyphilitic individuals. These individuals are considered in the study of untreated syphilis in the male Negro which has been in process in Macon County, Alabama, since 1932.[1-9] This is familiarly referred to as the Tuskegee Study.

A vast literature has grown up dealing with the pathologic lesions attributed to syphilis. The pathogenesis of certain of the classic syphilitic lesions has been adequately studied and explained. However, there remained, when this study was begun, many gaps in knowledge of the end results of untreated syphilis. It was anticipated that some of remaining problems should be resolved.

No reports of other prospective studies of the end results of untreated syphilis are yet available.

In 1929, Bruusgaard[10] published an analysis of the outcome of the disease in a group of 473 patients at three to forty years after infection. For the first time, data were available to suggest the probability of spontaneous cure, continued latency, or serious or fatal outcome. The Bruusgaard group presently is being restudied with the addition of further autopsy data.[11]

With the appearance of the Bruusgaard paper, the significance of his material was immediately recognized, but certain questions were left unanswered. Plans then were slowly taking shape in the United States for the later development of a national program to control syphilis. It was realized that numerous questions about the natural history and course of syphilis needed answering to provide the necessary scientific background for a program of public health control. As a result of certain factors discussed elsewhere,[12] there was initiated in 1932 in Tuskegee, Alabama, the long-term program of observation of a group of male Negroes with untreated syphilis and a matching control group. The objective was the observation of all individuals through life and to autopsy.

The twenty-year mark, 1952, has passed. By now about one-third of the group originally entered has died; it is anticipated that for the remainder to expire will require at least another twenty years. It is desirable, therefore, to take stock of the findings at this point. We can make available to other workers the results we have noted so that they may be translated into medical and public health practice at once. It is felt that the experience thus far provides important information with particular reference to the effects of syphilis itself. In the years to come, the force of mortality associated with aging will tend to obscure the possible effects of syphilis. This has been shown in the study of life expectancy of this group.[5]

The group now under study consists of 408 syphilitic patients and 192 presumably nonsyphilitic patients. The presence or absence of syphilis at time of entry to the study group was based on medical history, physical examination, and serologic tests of the blood and spinal fluid. Clinical information, collected at periodic examinations during the twenty years the study has been in progress, has furnished evidence that morbidity in a group of untreated male Negroes exceeds that in a nonsyphilitic group, and that abnormal x-ray and fluoroscopic measurements of the heart and aorta occur more frequently in the adult male Negro with untreated syphilis.[3] Life tables constructed on the basis of twenty years of mortality experience in the two groups show that the life expectancy of the Negro man of age 25 to 50 years with untreated syphilis is reduced by about 17 per cent.[5]

To secure the necessary pathologic data, the assistance of the Milbank Memorial Fund was generously offered. This assistance has continued through the present time, permitting the maintenance of a flexible and highly personal program activity in research which would be legally impossible if government funds were to be used, and giving a promise of continuity of support which is vital for such a program. Fees for autopsies and other expenses which official agencies were not able to assume were paid for by the Fund.

However, financial support is only one of the many difficulties involved in securing accurate post-mortem information. The warm climate in this region,

together with the practice of holding bodies for long periods before burial, while relatives assemble, often makes it necessary to embalm the bodies at least by arterial injection before the autopsies are performed. Poor communication facilities contribute to the delay in the examination of fresh tissues. None of the undertaking establishments has refrigeration, and the post-mortem examinations often are made under inconceivably adverse circumstances. Following each gross examination, specimens of the vital organs together with a protocol of the gross findings are forwarded to the Laboratory of Pathology, National Institutes of Health, for microscopic examination.

In the analysis presented in this report, an attempt will be made to determine the extent of agreement in the gross and microscopic findings in relation to the effects of syphilitic infection on the human body and to correlate both types of findings with the clinical and serologic information obtained at the several physical examinations performed on the individual prior to death. Since the validity of such a correlation, especially when it involves conclusions indicating differences among syphilitic and nonsyphilitic patients, depends to a large extent on the accuracy and consistency of the basic data, it might be well to point out some of the following important considerations:

(a) All individuals in the original study group are male Negroes, 25 years of age or older. The syphilitic group was selected first, and the control patients were chosen in such a manner as to obtain comparable age distribution in the two groups.

(b) At the beginning of the study, the 408 syphilitic patients gave a history of infection, with a penile scar as added evidence of infection in some cases, and had at least two positive blood tests for syphilis, or a positive spinal fluid.

(c) Over the twenty-year period all fluoroscopic examinations have been made by one radiologist (Peters), who also has performed most of the gross autopsy examinations. Preparation of histopathologic material has been done by various pathologists at National Institutes of Health during the period of investigation. For purposes of this study, review of each of the gross examinations and of all available microscopic sections of the aortas has been done by one pathologist (Peers) without prior knowledge by him of the patient's history with respect to the presence or absence of syphilis.

(d) The establishment of a syphilitic and a control group by definite criteria at a specific time and the following of each individual clinically and serologically to the time of autopsy has obviated the necessity of doing any portion of the study in retrospect.

During the years 1933 to 1952, 216 of the study group have died: 165 (40 per cent) of the 408 in the syphilitic group, and 51 (27 per cent) of the 192 in the control series. Autopsy has been obtained on 92 (56 per cent) of the deceased syphilitic patients as compared to 33 (65 per cent) of the nonsyphilitic patients who have died. However, no significant differences could be demonstrated in the age of distribution of those autopsied in the two groups (Table I). The fact that age is an equal factor in both groups tends to eliminate from consideration the aging process in accounting for some of the differences in pathologic findings among patients in the study group.

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TABLE I. NUMBER AND PERCENTAGE DISTRIBUTION OF SYPHILITIC AND CONTROL PATIENTS EXAMINED AT AUTOPSY, BY AGE AT TIME OF DEATH

AGE AT TIME OF DEATH (YR.)	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
25-34	2	2.2	2	6.2
35-44	4	4.3	1	3.1
45-54	15	16.3	3	9.4
55-64	26	28.3	10	31.2
65-74	24	26.1	8	25.0
75-84	16	17.4	5	15.6
85-94	4	4.3	3	9.4
95 or more	1	1.1	—	—
All ages	92	100.0	32	100.0
Per cent under 65 yr.	51.1		50.0	
Per cent 65 yr. and older	48.9		50.0	
Median age at death	64.5 yr.		63.5 yr.	

CARDIOVASCULAR SYPHILIS

A detailed study of the gross and microscopic autopsy findings on the individuals included in this study indicates that most of the lesions characteristic of syphilitic involvement are to be found in the cardiovascular system. Of the ninety-two syphilitic patients examined post mortem, gross and microscopic findings relative to the cardiovascular system for eighty-nine patients were available for analysis.

Gross Autopsy Examination.—Since one of the major purposes of this study is to investigate the extent to which syphilitic involvement can be measured by gross and microscopic autopsy findings, it seemed advisable to set up diagnostic criteria which would lend consistency and objectivity to the interpretation of the recorded material. While the incidence and description of the gross findings are, of necessity, based on the interpretations recorded by the prosector, the records of the gross examinations have been reviewed and the following conditions have been considered in determining the presence or absence of cardiovascular syphilitic involvement:

(a) Linear striation of the thoracic aorta. Small depressed lineations parallel the long axis of the vessel which may be seen anywhere throughout the aortic length, but which are more numerous and more prominent in the proximal inch of the aorta.

(b) Pearly white scarring of the subintima of the aorta.

(c) Diminution of the elasticity of the aorta in both longitudinal and transverse directions. This observation may be noted where little or no intimal change is apparent.

(d) Fusiform dilatation between the level of the cusps and the junction of the innominate artery, generally on the anterior or anterolateral aspect and disproportionate to any enlargement of the remainder of the aortic lumen.

TABLE II. INCIDENCE BY AGE GROUPS OF ABNORMAL GROSS FINDINGS IN THE AORTAS OF EIGHTY-NINE SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

	SYPHILITIC PATIENTS						CONTROL PATIENTS					
	NUMBER			PER CENT			NUMBER			PER CENT		
	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER
Number of patients examined	89	46	43	—	—	—	32	16	16	—	—	—
Linear striation of thoracic aorta	29	16	13	32.6	34.8	30.2	2	1	1	6.3	6.2	6.2
Pearly intimal scars	26	12	14	29.2	26.1	32.6	6	1	5	18.8	6.2	31.2
Diminution of elasticity	10	3	7	11.2	6.5	16.3	2	—	2	6.3	—	12.5
Fusiform dilatation	40	16	24	44.9	34.8	55.8	14	5	9	43.8	31.2	56.2
Saccular aneurysm of thoracic aorta	7	6	1	7.9	13.0	2.3	—	—	—	—	—	—

(e) Saccular aneurysm, where the dilatation is of sufficient proportions to divert the blood outside the lumen of the aorta, or a widening of sufficient dimensions to produce clot formation and recanalization of the blood flow.

(f) Valvular changes consisting of thickening and rolling of the free edge of the aortic cusps and separation of the valve cusps at the commissures.

On the basis of these criteria, syphilitic aortitis or saccular aneurysm, the most important major manifestations of syphilitic infection, was diagnosed grossly at autopsy in thirty-six (40 per cent) of the eighty-nine patients. From Table II, in which the comparative incidence of the listed criteria among the syphilitic and nonsyphilitic patients is presented, it will be noted that the most reliable gross sign of syphilitic aortitis in this group of patients seems to be linear striation of the intima of the thoracic aorta, a condition found to be present in twenty-nine of the aortas diagnosed as syphilitic. The reliability of this condition as a criterion of syphilitic involvement is based on the facts that definite evidence of this striation was not noted in any case among the syphilitic group where syphilis was not microscopically diagnosed and that only twice was it noted in the thirty-two control patients examined post mortem.

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Fusiform dilatation of the thoracic aorta was the most frequent sign of syphilitic involvement, being noted in forty (44.9 per cent) of the aortas in the syphilitic group. However, this dilatation was not considered to be pathognomonic of syphilis since it was found to be present to some degree in four of the aortas in the syphilitic group where, in the absence of other criteria, a diagnosis of syphilitic involvement was not warranted. Furthermore, fusiform dilatation was noted in fourteen (43.8 per cent) of the aortas in the control group, and in six instances was accompanied by moderate or extreme arteriosclerosis, a condition which could result in weakening and stretching of the aortic wall. Intimal scars described as pearly and gross diminution of elasticity were noted somewhat more frequently in the aortas of the syphilitic group than in those of the control group, but the difference in incidence was not marked enough to establish them as reliable diagnostic criteria.

Saccular aneurysm of the thoracic aorta, generally considered to be a pathognomonic lesion of syphilis, was found in only seven of the syphilitic series. Of these, one was small and single, three were small and multiple, two were large enough to have encroached upon and caused bone erosion in the thoracic cage, and one, although small, was the immediate cause of death by rupture into the pericardial sac with cardiac tamponade. No saccular aneurysms were found among the control group. Dissecting aneurysm, a lesion considered to be of arteriosclerotic origin, was found once in the syphilitic and twice in the control group. A single case of aneurysm of the upper abdominal aorta was found in the syphilitic group. In this patient the aorta showed gross arteriosclerosis of an extreme grade and microscopically mild lesions of syphilis; and consequently the aneurysm was considered to be arteriosclerotic in origin.

The findings of gross changes in the aorta must be considered with respect to age as a possible causative factor as well as syphilis. In Table II, a further breakdown of the findings with respect to age is shown. Since the group is not large enough to allow for detailed division, the age of 65 is taken as a significant

landmark. It will be seen that the finding considered along with saccular aneurysm of the thoracic aorta as most highly pathognomonic of syphilis, namely, linear striation of the thoracic aorta, is apparently unaffected by age. In other words, the process appears to be not a result of aging, but instead closely related to syphilis. The other processes, except for saccular aneurysm, show increases with increasing age, which suggests a probable close relationship to the process of aging with attendant changes in structure and function.

Microscopic Examination.—Diagnoses of cardiovascular syphilis on the basis of microscopic findings were made in essentially the same manner as the gross diagnoses, with the pathologist unaware of the presence or absence of history of syphilitic infection and on the basis of diagnostic criteria set up prior to the review of the records. A complete review of the microscopic sections of the aortas was made in light of these diagnostic criteria:

(a) Gross thickening of the aortic wall. Seen easily, when the stained section is viewed with the naked eye, as a fairly uniform thickening of the entire length of the section up to 3 to 5 mm. with blurring of the normal layers. A section of normal aorta so seen appears chiefly as the thin (1 to 2 mm.), uniform, densely stained, medial coat. The arteriosclerotic aorta shows a distinct media and a thickened intima, very irregular in both width and density due to patchy deposition of atheromatous material.

(b) Necrosis of the media. An uncommon but very significant finding consists of irregular stellate or elliptical streaks of infarct type necrosis with nuclear fragmentation in the media, presumably due to occlusion of vasa vasorum, and hence of the nature of miliary gummas.

(c) Fibrosis of the adventitia. In minor degree this is, of course, a subjective interpretation, but when well marked the adventitia is broadened, contributing much to the gross thickening mentioned previously, and the normal loose areolar tissue is converted to quite coarsely fibrous and sometimes partly hyalinized connective tissue.

(d) Scarring of the media. Represents either a healed stage or a lesser degree of the ischemic necrosis noted previously. The elastic laminae of the media are deficient in streaks and patches and replaced by collagenous tissue in which there are often prominent, somewhat dilated, capillary vessels.

(e) Intramural perivascular infiltration consisting of accumulation of variable number of small lymphocytes and some plasma cells about vessels in the media, often those present in medial scars. Some degree of such infiltration also is common in vessels in the somewhat thinned portion of the media underlying large atheromatous masses in the intima.

(f) Thickening of the vasa vasorum. This consists occasionally of endothelial proliferation but more commonly of hyaline fibrosis, greatly thickening the wall and reducing the lumen of the vasa vasorum. It is usually of spotty distribution, often only a few vasa vasorum in a given section being thickened while the remainder appears normal. It cannot be clearly separated from arteriolosclerosis accompanying essential hypertension, and some of the incidence in both syphilitic and control groups may have been due to this common complication.

(g) Adventitial perivascular infiltration. Perhaps "paravascular" infiltration would be a better term for this traditional but unreliable lesion of syphilis. Variable numbers of small lymphocytes and plasma cells are found grouped in relation to adventitial vessels, but more often in patches or small streaks to either side than arranged in a circle about them.

The incidence of these conditions among the syphilitic and control patients is shown in Table III, in order by increasing frequency and correspondingly decreasing specificity. Only two conditions, gross thickening of the aortic wall and necrosis of the media, appeared to be pathognomonic of syphilis, and these two lesions, considered to represent advanced active disease, were in every case accompanied by some of the other microscopic criteria described previously. The increased incidence of the two conditions among the individuals under 65 years of age is added evidence that these lesions are related to the syphilitic rather than the aging process.

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In interpreting microscopic slides, some degree of subjective variation is unavoidable, but in general a diagnosis of syphilitic aortitis was made only if two or more of the criteria definitely were present. As noted previously, the histopathologic diagnoses were made and recorded by the pathologist without knowledge of the syphilitic status of the patients. On this basis, syphilitic aortitis was diagnosed in forty-one (46.0 per cent) of the patients in the syphilitic group and in four (12.5 per cent) of those in the control series. However, in the latter series, three of the lesions were doubtful, and one minimal, while those in the syphilitic group consisted of five doubtful, twelve minimal, ten moderate, and fourteen severe.

The attempt to grade the severity of syphilitic involvement of the aorta into four degrees was, like all such attempts at rough quantitation of biologic phenomena, merely an artificial division into four groups of what was actually a continuous spectrum of disease process ranging from the minimal recognizable damage to the most severe, extensive, and fully developed lesions. This grading, however, appears to have some validity since only minimal changes conceivably due to syphilis were observed in the control group, while 60 per cent of the syphilitic group with microscopically diagnosed syphilis presented lesions that were moderate or, even more often, severe.

Comparative Results of Gross and Microscopic Examinations.—The microscopic diagnosis of syphilitic aortitis proved to be slightly more sensitive than the gross diagnosis. Among the eighty-seven aortas examined by both methods, forty were diagnosed microscopically and thirty-five, grossly. In the syphilitic series of cases, the gross and microscopic diagnoses agreed in establishing the presence or absence of syphilitic involvement in sixty-two (71.3 per cent) of the eighty-seven diagnoses compared (in two patients either the gross description or the microscopic material was inadequate for diagnostic purposes). It will be noted from Table IV that in ten instances the gross diagnosis of syphilitic aortitis was not confirmed by the microscopic examination. In two of these the microscopic material, a single slide, was probably insufficient to rule out syphilis. In the remaining eight patients, one almost certainly had arteriosclerosis wrongly interpreted as syphilis, one diagnosis was based on minimal

TABLE III. INCIDENCE, BY AGE GROUPS, OF ABNORMAL MICROSCOPIC FINDINGS IN THE AORTAS OF EIGHTY-NINE SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

	SYPHILITIC PATIENTS						CONTROL PATIENTS					
	NUMBER			PER CENT			NUMBER			PER CENT		
	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER	TOTAL	UNDER 65	65 AND OLDER
Number of patients examined	89	46	43				32	16	16			
Gross thickening of aortic wall	12	7	5	13.5	15.2	11.6	—	—	—	0	0	0
Necrosis of the media	7	5	2	7.9	10.9	4.7	—	—	—	0	0	0
Fibrosis of the adventitia	28	13	15	31.5	28.3	34.9	3	2	1	9.4	12.5	6.3
Medial scars	30	15	15	33.7	32.6	34.9	4	1	3	12.5	6.2	18.8
Intramural perivascular infiltration	33	17	16	37.1	37.0	37.2	5	2	3	15.6	12.5	18.8
Thickened vasa vasorum	37	20	17	41.6	43.5	39.5	6	3	3	18.8	18.8	18.8
Adventitial perivascular infiltration	58	30	28	65.2	65.2	65.1	13	6	7	40.6	37.5	43.8

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evidence of syphilis in the form of a few longitudinal striae, and in the other six patients there was moderate to extreme arteriosclerosis with scarring and some dilatation of the aorta which had been attributed to syphilis rather than to arteriosclerosis. From the same table it is apparent that the diagnosis of syphilitic aortitis in fifteen patients was made by microscopic examination alone, but in ten of these the lesions were minimal or doubtful and would not have been expected to be accompanied by gross changes. In thirty-seven (41.6 per cent) of the syphilitic group, there was neither gross nor microscopic evidence of syphilitic aortitis, and in twenty-five patients (28.1 per cent), aortitis was diagnosed by both gross and microscopic findings.

TABLE IV. COMPARISON OF THE INCIDENCE OF SYPHILITIC INVOLVEMENT OF THE CARDIOVASCULAR SYSTEM AS DIAGNOSED FROM GROSS AND MICROSCOPIC FINDINGS AMONG EIGHTY-SEVEN SYPHILITIC PATIENTS EXAMINED AT AUTOPSY

MICROSCOPIC EXAMINATION DIAGNOSIS	GROSS EXAMINATION DIAGNOSIS	
	CARDIOVASCULAR SYPHILITIC INVOLVEMENT	NO CARDIOVASCULAR SYPHILITIC INVOLVEMENT
Cardiovascular syphilitic involvement	25	15
Doubtful	—	5
Minimal	7	5
Moderate	5	4
Severe	13	1
No cardiovascular syphilitic involvement	10	37

Aortitis in Relation to Positive Serologic Tests.—Of the eighty-seven patients in whom the aorta was examined both grossly and microscopically, sixty had positive blood serologic tests for syphilis when last tested (Kahn qualitative) prior to death, three had doubtful tests, and twenty-four showed negative results (Table V). Of the sixty with positive tests, twenty-three were diagnosed by both gross and microscopic methods as having syphilitic aortitis, five by gross examination only, and nine by microscopic examination only. If, in order to be conservative, it is assumed that none of the fourteen with only gross or only microscopic evidence, and thus possibly nonsyphilitic, had true syphilitic involvement, the minimum incidence of cardiovascular syphilis among persons with sustained seropositivity from time of entry to study until death would be 38 per cent. On the other hand, if all fourteen of those with a possible questionable diagnosis had syphilitic involvement, the maximum incidence of cardiovascular syphilis in this same group would be 62 per cent. On the basis of these two estimates of the incidence of aortitis in the group coming to autopsy, it is suggested that a Negro male with syphilis of more than ten years' duration for which he had received no treatment (or less than 12 units of routine treatment when a unit is defined as one injection of an arsenical or two of bismuth) and with sustained seropositivity prior to death would have roughly a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy.

TABLE V. THE INCIDENCE OF SYPHILITIC AORTITIS AS DIAGNOSED BY GROSS AND/OR MICROSCOPIC EXAMINATION IN RELATION TO SEROLOGIC STATUS PRIOR TO DEATH

RESULTS OF LAST SEROLOGIC TEST PRIOR TO DEATH (KAHN QUALITATIVE)	TOTAL CASES EXAMINED	GROSS AND MICROSCOPIC	GROSS ALONE	MICROSCOPIC ALONE	ABSENCE OF AORTITIS ESTABLISHED BY GROSS AND MICROSCOPIC
Positive	60	23	5	9	23
Doubtful	3	—	—	—	3
Negative	24	2	5	6	11
Total	87	25	10	15	37

The presence of aortitis was not confirmed by either gross or microscopic examinations in the three patients with doubtful serologic test on the blood at last test prior to death. Of the twenty-four negative serologic tests prior to death, only two individuals were diagnosed both grossly and microscopically as having syphilitic aortitis by either gross or microscopic examination. The remaining eleven seronegative individuals showed freedom from syphilitic aortitis by both gross and microscopic means.

Cardiac Hypertrophy.—The heart of the patient with syphilis may be enormously enlarged, moderately enlarged, or not enlarged at all. With the exception of syphilitic valvulitis, there is no gross finding of sufficient specificity to justify a diagnosis of hypertrophy due to syphilitic involvement. Considering as hypertrophied all hearts weighing 400 grams or more, it was found that forty-eight (69.5 per cent) of the sixty-nine hearts weighed at autopsy among the syphilitic patients were enlarged as compared to eighteen (69.2 per cent) of the twenty-six weighed in the control group. On the basis of the equal incidence of cardiac hypertrophy in the two groups, it would seem that in this study group, at least, the abnormality is not related to syphilitic involvement. In attempting to account for the high incidence of cardiac enlargement in the study population, the presence of other abnormal conditions, including hypertension, was investigated. Among those whose heart weight was less than 400 grams, 20.7 per cent had systolic blood pressures of 160 mm. of mercury or more when last examined prior to death as compared to 54.7 per cent of those where the heart weight was 400 grams or more. Diastolic pressures of 95 mm. of mercury or more were found in 37.9 per cent of those with heart weight less than 400 grams and in 54.7 per cent of those with heart weight of 400 grams or more. The massively hypertrophied hearts weighing over 600 grams were found decidedly more often in the control group. By the most liberal interpretation of the autopsy records, slightly less than 10 per cent of the entire syphilitic group showed aortic valve lesions suggestive of syphilis, and only one-half of these were reasonably pathognomonic. In the combined groups of syphilitic and control patients there were no instances of rheumatic valvulitis, congenital anomaly, or pericardial adhesions. Thus, it would seem that syphilis played a minor role in the causation of cardiac

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hypertrophy and that the principal etiological factors probably were hypertension and/or myocardial degeneration and compensatory hypertrophy. The degrees of longevity and of physical activity in these patients with massive hypertrophy are remarkable, as discussed elsewhere.[6,7]

The Incidence of Arteriosclerosis.—The similarity of the cardiovascular signs of arteriosclerosis and syphilitic aortitis has led to much speculation regarding the degree of coincidence of the two conditions. Clinicians are in agreement that if syphilis predisposes to severe arteriosclerosis or is responsible for premature arteriosclerotic involvement, pathologic evidence is needed before such a premise can be accepted.

The incidence of arteriosclerosis as detected by gross examination among the syphilitic and nonsyphilitic patients by age at time of death is shown in Table VI. On cursory examination, the number of cases of advanced arteriosclerosis among those patients under 55 years of age in the syphilitic group is quite startling but, due to the smallness of the number examined among the younger individuals, the difference in the incidence of arteriosclerosis among the younger individuals in the two groups is not statistically significant. The increased proportion of severe arteriosclerosis in both the syphilitic and the nonsyphilitic groups with the progression of age is to be expected in view of the known correlation of arteriosclerosis with age. The grading or degree of involvement is subject to the same general considerations as discussed with respect to syphilitic involvement earlier in this paper.

Clinical Findings Related to Autopsy Findings.—In the correlation of clinical findings prior to death with the gross and microscopic autopsy findings, only those cases were used where both gross and microscopic examinations were in agreement in establishing or ruling out the presence of syphilitic involvement. This selection of cases was necessary since clinical diagnostic methods could not be expected to detect minimal changes which could be diagnosed only by microscopic methods nor did it seem reasonable to attempt to correlate clinical findings with gross diagnoses which had not been verified by microscopic methods. Presented in Table VII is a summary of the clinical findings including those diagnosed by x-ray and fluoroscopic methods in relation to gross and microscopic findings among the selected group of syphilitic individuals described previously.

In the gross and microscopic autopsy examination, two aortas were found to have syphilitic involvement where none had been noted by physical examination or x-ray examination. In one of these instances a clinical diagnosis of aortic abnormality and cardiac hypertrophy (the heart weighed 1,000 grams at autopsy) due to rheumatic heart disease was recorded. In the other patient the aorta was described as normal at the last examination prior to death; however, this examination was performed in 1938 and the patient died in 1948, a ten-year interval during which aortic involvement might well have become manifest.

The presence of six of the seven saccular aneurysms found at autopsy had been detected by clinical means prior to death. The patient in whom the diagnosis was not made was seen only at the time of the initial physical examination

TABLE VI. THE INCIDENCE OF ARTERIOSCLEROSIS AMONG SYPHILITIC AND NONSYPHILITIC PATIENTS BY DEGREE OF INVOLVEMENT AND AGE AT TIME OF DEATH

AGE AT TIME OF DEATH (YR.)	SYPHILITIC PATIENTS					NONSYPHILITIC PATIENTS				
	NONE OR DOUBTFUL	MINIMAL	MODERATE	SEVERE	NOT EXAMINED	NONE OR DOUBTFUL	MINIMAL	MODERATE	SEVERE	NOT EXAMINED
25-34	2	—	—	—	—	1	—	—	—	1
35-44	2	1	1	—	—	—	1	—	—	—
45-54	2	5	6	2	—	1	1	—	—	1
55-64	1	8	9	4	1	1	1	3	4	1
65-74	2	3	13	4	—	—	1	—	6	—
75-84	—	2	9	6	—	—	1	3	2	—
85-94	—	1	3	1	—	—	—	—	2	1
95 or older	—	—	1	—	—	—	—	—	—	—

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in 1932 and was described at that time as having a marked fusiform aortic dilatation. Since death did not occur until four years later, in 1936, this too could have been an instance where the aneurysm developed during the interval between physical examination and death. It has been possible for one of the authors (Peters) to observe in a series of four syphilitic patients the gradual progression from normal aortic configuration through dilatation to development of aneurysm.

TABLE VII. COMPARISON OF CLINICAL DIAGNOSES INVOLVING THE AORTA PRIOR TO DEATH WITH DIAGNOSES BASED ON GROSS AND MICROSCOPIC FINDINGS AMONG SIXTY-TWO SYPHILITIC PATIENTS AMONG WHOM THE GROSS AND MICROSCOPIC DIAGNOSES WERE IN AGREEMENT

CLINICAL DIAGNOSIS PRIOR TO DEATH	GROSS AND MICROSCOPIC DIAGNOSIS		
	SYPHILITIC AORTITIS	SACCULAR ANEURYSM	NO SYPHILITIC AORTIC INVOLVEMENT
Syphilitic aortitis	16	1	19
Saccular aneurysm	—	6	—
No syphilitic aortic involvement	2	—	18
Total	18	7	37

The nineteen patients in whom aortitis was diagnosed clinically, yet in whom the gross and microscopic examinations ruled out the presence of syphilitic involvement of the aorta, offer proof of the fact that clinical methods are effective in the detection of abnormality but inadequate in the determination of etiology. Eight of the nineteen patients diagnosed with aortitis by clinical methods only were described at gross examination as having arteriosclerosis with fusiform dilatation of the aorta, one patient was found to have a dissecting aneurysm, nine were described as having moderate or severe arteriosclerosis, and only one patient was reported as completely negative for arteriosclerosis.

CENTRAL NERVOUS SYSTEM INVOLVEMENT

The central nervous system (brain and portion of spinal cord) was examined in forty-six of the syphilitic patients and in thirteen of the control patients (Table VIII). Of the forty-six brains of syphilitic patients, twenty-eight were found to be essentially normal, six showed one or more areas of arteriosclerotic softening, five showed cerebral hemorrhage, including one traumatic hemorrhage secondary to skull fracture, and one toxic petechial hemorrhage apparently secondary to lobar pneumonia. An abscess secondary to bacterial endocarditis was found in one instance. Of the twenty-nine patients in whom sclerosis of the major arteries was detected, only three were sufficiently advanced to be especially noted. Only two brains of the forty-six examined showed definite syphilitic involvement, the one meningovascular syphilis, and the other paresis. Both of the patients with definite involvement died as inmates of the state insane hospital. The patient with meningovascular syphilis showed only minimal

microscopic evidence of aortitis, but the paretic patient showed a typical full-blown gross and microscopic picture of syphilitic aortitis. The great scarcity of frank syphilitic involvement of the central nervous system and the complete absence of lesser lesions attributable to syphilis are noteworthy.

TABLE VIII. INCIDENCE OF ABNORMAL CONDITIONS IN THE CENTRAL NERVOUS SYSTEM AMONG FORTY-FOUR SYPHILITIC AND THIRTEEN CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Opacity of pia-arachnoid	9	20.5	1	7.7
Focal softening of cortex	5	11.4	—	—
Focal softening of white matter	2	4.5	—	—
Cerebral hemorrhage	5	11.4	1	7.7
Sclerosis of major arteries	29	65.9	6	46.2
Microscopic cortical atrophy	2	4.5	—	—
Cellular infiltration, perivascular and meningeal	7	15.9	1	7.7
Perivascular iron pigment	2	4.5	—	—
Glial nodules on the ependyma	1	2.3	1	7.7

Of the thirteen brains from control patients examined, nine were essentially normal. Two of the six patients showing arteriosclerosis had damage severe enough to be especially noted; one showed cerebral hemorrhage and another edema secondary to head injury. A mild degree of grossly visible thickening of the pia-arachnoid was noted in a few cases in both syphilitic and control series, but it could not be correlated with microscopic lesions and was of no apparent pathologic significance.

While only two of the forty-six syphilitic patients having examinations of the brain and spinal cord showed unequivocal evidence of syphilitic involvement of the central nervous system, comparison between syphilitic and nonsyphilitic groups (the material presented in Table VIII) reveals a higher proportion of abnormal findings in the syphilitic group. However, no particular significance can be attached to these findings due to the small number of brain examinations made at autopsy, especially among the controls.

OTHER SYSTEMS OF THE BODY

From the findings of this study, it would seem that the systems of the body, other than the cardiovascular and the central nervous systems, are not commonly affected by syphilitic infection. In Table IX is shown the comparative incidence of pertinent findings in the respiratory system in the two groups of patients. While fibrosis of the lung was found more often among the ninety-two syphilitic patients and pleural effusion was present to a greater extent among the thirty-two control patients, neither difference showed statistical significance. The incidence of hypostatic or bronchopneumonia was high in both groups, and was a terminal illness in patients for whom the primary cause of death was assigned to other disease processes.

TABLE IX. INCIDENCE OF ABNORMAL CONDITIONS IN THE RESPIRATORY SYSTEM AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Stenosis or destruction in respiratory system	1	1.1	—	—
Scars, masses, or cavities in lung—tuberculous	6	6.5	2	6.2
Scars, masses, or cavities in lung—nontuberculous	4	4.3	—	—
Lobar pneumonia	4	4.3	4	12.5
Hypostatic or bronchopneumonia	43	46.7	11	34.4
Pleural effusion	48	52.2	20	62.5
Fibrosis of lung	38	41.3	9	28.1
Malignant tumors	—	—	2	6.2

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It will be noted from Table XIII that four of the syphilitic group died from diseases involving the gastrointestinal system. In each instance, only laboratory evidence of syphilis was noted and no clinical symptoms of syphilitic involvement were present prior to death. At autopsy, one patient showed diffuse cirrhosis of the liver; another, fatty infiltration of the liver; the third patient, a pancreatic cyst and hemangioma of the liver; and the fourth, peptic ulcer with fatty infiltration of the liver. While some involvement of the liver was noted in each of these cases, the morbid processes could not be directly attributed to syphilitic infection.

Fibrosis of the pancreas, thought by some investigators (as reviewed by Rosahn[13]) to be one of the characteristic lesions of late syphilitic involvement, was noted in five of the syphilitic group at autopsy. In one instance, the fibrosis was associated with a duodenal ulcer, and in another, arteriosclerotic changes were thought to have taken place. The remaining three patients exhibited fibrosis which could not be attributed to a nonsyphilitic cause. However, all five patients, representing the presence of fibrosis in 5.3 per cent of the syphilitic group, do not constitute a significantly higher incidence in the syphilitic population. In all, only slight differences in the incidence of abnormal gastrointestinal findings were noted among the syphilitic and the nonsyphilitic patients (Table X).

Comparatively few abnormal findings were found at autopsy in the hematopoietic and endocrine systems. Capsular opacity and thickening of the spleen, the only findings of any consequence, were present at about the same degree in both the syphilitic and the control groups. A sickle-cell trait was exhibited in approximately 3 per cent of each group (Table XI).

The incidence of glomerulonephritis, pyelonephritis, and cystitis was higher among the syphilitic patients, but in each instance the difference between the number of urinary infections in the two study groups is less than that which could be attributed to chance occurrence. More than 50 per cent of both groups showed some degree of arteriosclerotic involvement of the urinary system, and in many cases this involvement led to renal failure and death.

Atrophy and scarring of the testis have been considered by some authorities to be pathognomonic of syphilitic infection. In this study, atrophy was noted

in almost 50 per cent of each of the study groups (Table XII). Since roughly 50 per cent of each group were 65 years of age or older at time of death, it seemed quite possible that testicular atrophy might be merely an aging process in this population. On investigation, this assumption was considered to be valid in that 31 per cent of the syphilitic patients and 29 per cent of the control patients under 65 years exhibited the condition, as compared to 65 per cent of each group among those 65 years and older. Scarring of the testis was noted in six individuals, all of them in the syphilitic group; in one instance, however, the condition was thought to be a tuberculous process. At any rate, the incidence of the lesion among the syphilitic patients is within the limits of chance.

TABLE X. INCIDENCE OF ABNORMAL CONDITIONS IN THE DIGESTIVE SYSTEM AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Esophageal varices	—	—	—	—
Atrophy of the gastric mucosa	—	—	—	—
Chronic gastritis	1	1.1	1	3.1
Peptic ulcer	3	3.3	—	—
Malignant tumors of gastrointestinal tract	3	3.3	1	3.1
Rectal stricture	—	—	—	—
Fatty infiltration of liver	21	22.8	9	28.1
Gross scarring of liver (hepar lobatum)	4	4.3	2	6.2
Gumma of liver	—	—	—	—
Diffuse cirrhosis of liver	14	15.2	6	18.8
Fibrosis of pancreas	5	5.4	—	—

TABLE XI. INCIDENCE OF ABNORMAL CONDITIONS IN THE HEMATOPOIETIC AND ENDOCRINE SYSTEMS AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Hematopoietic system:				
Enlargement of spleen	10	10.9	2	6.2
Infarct of spleen	2	2.2	—	—
Capsular opacity and thickening of spleen	36	39.1	12	37.5
Sickle-cell trait	3	3.3	1	3.1
Blood dyscrasias (leukemia)	1	1.1	—	—
Endocrine system:				
Pituitary pathologic changes	—	—	1	3.1
Thyroid hyperplasia—diffuse	1	1.1	—	—
Thyroid hyperplasia—nodular	—	—	—	—
Adrenal pathologic changes	5	5.4	3	9.4

In this particular study group it was difficult to establish the presence of syphilitic involvement by means of external post-mortem examination. Alopecia

areata, while fairly prevalent in the group, was not sufficiently defined to differentiate the syphilitic from the control patients. Osteitis was noted in four (4 per cent) of the syphilitic group, but was not severe or extensive enough to establish definitely that it was of syphilitic origin. Pigmented scars were frequently seen over the anterior aspects of the legs. However, they could not be distinguished in many patients from healed varicose ulcerations or from similar scarred areas resulting from long exposure to the heat of an open fireplace, a common method of heating in the study area. Where pigmentation of the palms of the hands was found it was difficult to determine if the pigmented areas were healed lesions of secondary syphilis or were caused by long exposure to the sun. Enlarged lymph nodes were found with equal frequency in the two groups.

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TABLE XII. INCIDENCE OF ABNORMAL CONDITIONS IN THE URINARY AND REPRODUCTIVE SYSTEMS AMONG NINETY-TWO SYPHILITIC AND THIRTY-TWO CONTROL PATIENTS EXAMINED AT AUTOPSY

ABNORMAL CONDITION	SYPHILITIC PATIENTS		CONTROL PATIENTS	
	NUMBER	PER CENT	NUMBER	PER CENT
Urinary system:				
Arteriosclerotic atrophy of kidney	1	1.1	—	—
Arteriosclerosis—benign	52	56.5	16	50.0
Arteriosclerosis—malignant	1	1.1	1	3.1
Glomerulonephritis	18	19.6	4	12.5
Pyelonephritis	22	23.9	3	9.4
Cystitis	15	16.3	5	15.6
Malignant tumors	—	—	—	—
Reproductive system:				
Prostatic hypertrophy	59	64.1	18	56.2
Atrophy of testis	43	46.7	15	46.9
Scarring of testis	5	5.4	—	—
Gumma of testis	—	—	—	—
Stricture of urethra	2	2.2	—	—
Malignant tumors	5	5.4	—	—

RELATIONSHIP OF CLINICAL DIAGNOSIS TO PRIMARY CAUSE OF DEATH

A general idea of the relationship of the clinical diagnosis prior to death and the primary cause of death as determined through autopsy examination can be gained from the material shown in Table XIII. The four patients (4 per cent of the syphilitic group) in whom no clinical evidence was noted, yet in whom cardiovascular syphilis was recorded as the disease process causing death, provided a rough estimate of the inefficiency of present clinical methods in the diagnosis of syphilitic cardiovascular conditions severe enough to cause death. Of the syphilitic group, fifty-two were clinically diagnosed with cardiovascular involvement; in twenty-one (40 per cent) of these patients the syphilitic process was determined by post-mortem examination to be the underlying cause of death. The eleven individuals having clinical evidence of central nervous system involvement included the following: three with clinical paretic symptoms, where

TABLE XIII. PRIMARY CAUSE OF DEATH BASED ON AUTOPSY FINDINGS AMONG THIRTY-TWO CONTROL PATIENTS AND AMONG NINETY-TWO SYPHILITIC PATIENTS BY CLINICAL SYPHILITIC DIAGNOSIS AND SEROLOGY STATUS PRIOR TO DEATH

PRIMARY CAUSE OF DEATH	CONTROL PATIENTS	SYPHILITIC PATIENTS—CLINICAL DIAGNOSIS AND SEROLOGY									
		NO CLINICAL EVIDENCE		CARDIOVASCULAR SYPHILIS		CNS SYPHILIS		CARDIOVASCULAR AND CNS SYPHILIS		BONE AND SKELETAL SYPHILIS	
		STS+	STS−	STS+	STS−	STS+	STS−	STS+	STS−	STS+	STS−
Cause related to syphilis:	—	4	—	18	2	1	2	—	1	—	—
Aortitis, associated with congestive heart failure	—	3	—	11	2	—	1	—	1	—	—
Aneurysm	—	1	—	6	—	—	—	—	—	—	—
Valvular disease	—	—	—	1	—	—	—	—	—	—	—
Paresis	—	—	—	—	—	1	1	—	—	—	—
Tabes dorsalis	—	—	—	—	—	—	—	—	—	—	—
Tuberculosis, respiratory	1	2	—	2	—	—	—	—	—	—	—
Tuberculosis, other	—	1	—	—	—	—	—	—	—	—	—
Malignant neoplasm	4	5	—	2	1	—	—	1	—	—	—
Arteriosclerosis and degenerative heart disease	9	4	2	4	2	—	—	—	1	—	—
Hypertension	—	1	1	—	—	—	—	—	—	—	—
Vascular lesions of CNS	—	2	—	—	—	—	—	—	—	—	—
Pneumonia	1	—	—	—	—	—	—	—	—	—	—
Gastrointestinal disease	—	4	—	—	—	—	—	—	—	—	—
Renal failure	13	6	—	11	2	1	—	2	1	2	—
Motor vehicle accident	—	—	—	—	—	—	—	—	1	—	—
Other accidents	4	1	1	1	—	—	—	—	—	—	—
All causes	32	30	4	38	7	2	2	3	4	2	—

STS—Serologic test for syphilis.

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paresis was established as the cause of death in two cases, and cardiovascular syphilis in the other; eight in whom eye involvement, vascular changes, or tabetic symptoms or signs were noted, but who died of nonsyphilitic causes. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, does not seem to be different from that in the control group. Four of the control patients (12 per cent) as compared to nine of the syphilitic patients (10 per cent) died from cancer; one member of the control group (3 per cent) and six individuals in the syphilitic group (7 per cent) succumbed to tuberculosis.

SUMMARY

1. A study of the comparative incidence of the morphologic lesions found among ninety-two untreated syphilitic patients and thirty-two control patients examined at autopsy is presented.

2. The gross and microscopic findings on the individuals included in this study indicate that the lesions characteristic of syphilitic involvement in the Negro male are to be found for the most part in the cardiovascular system. For this reason, a detailed analysis of the cardiovascular abnormalities, including the relationship of clinical and autopsy findings, is included.

3. Linear striation of the thoracic aorta was found to be the most reliable gross sign of syphilitic aortitis, while thickening of the aorta wall and necrosis of the media were found to be pathognomonic of syphilitic aortitis in the microscopic examination.

4. In thirty-seven (41.6 per cent) of the eighty-seven syphilitic patients in whom the aorta was examined grossly and microscopically, there was no evidence of syphilitic aortitis by either examination, and in twenty-five (28.1 per cent) of the patients, aortitis was diagnosed by both gross and microscopic findings.

5. On the basis of the findings in this study, it is estimated that a Negro male with syphilis of more than ten years' duration for which he had received no treatment (or less than 12 units of routine treatment) and with sustained seropositivity prior to death would have, roughly, a 50-50 chance of demonstrating syphilitic cardiovascular involvement at autopsy.

6. The unusually high prevalence of cardiac hypertrophy in this study group is believed to be due to the presence of compensatory hypertrophy caused by hypertension and/or myocardial degeneration.

7. The similarity of the clinical signs and symptoms of syphilitic and arteriosclerotic aortitis reduces the efficiency of clinical methods in the detection of syphilitic aortitis.

8. The brain was examined in forty-six of the ninety-two syphilitic patients autopsied. The two patients showing clinical symptoms of central nervous system involvement (paresis and meningovascular syphilis) were among the group examined. The patient diagnosed with meningovascular syphilis showed microscopic cortical atrophy at autopsy, and both patients were found to have opacity of the pia-arachnoid and perivascular and meningeal cellular infiltration.

9. In the respiratory, digestive, hematopoietic, endocrine, urinary, and reproductive systems of the human body, the incidence of abnormalities among syphilitic patients was not significantly different from that among the control patients.

10. In twenty-eight (30.4 per cent) of the ninety-two syphilitic patients examined at autopsy, syphilitic involvement of the cardiovascular or the central nervous system was established as the primary cause of death. The distribution of the causes of death among the syphilitic patients, aside from syphilis itself, was not different from that in the nonsyphilitic group.

REFERENCES

1. Vonderlehr, R. A., Clark, T., Wenger, O. C., and Heller, J. R., Jr.: Untreated Syphilis in the Male Negro. A Comparative Study of Treated and Untreated Cases, J. Ven. Dis. Inform. **17**:260, 1936.
2. Heller, J. R., Jr., and Bruyere, P. T.: Untreated Syphilis in the Male Negro. II. Mortality During 12 Years of Observation, J. Ven. Dis. Inform. **27**:34, 1946.
3. Deibert, A. V., and Bruyere, M. C.: Untreated Syphilis in the Male Negro. III. Evidence of Cardiovascular Abnormalities and Other Forms of Morbidity, J. Ven. Dis. Inform. **27**:301, 1946.
4. Pesare, P. J., Bauer, T. J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro. Observation of Abnormalities Over 16 Years, Am. J. Syph., Gonor. & Ven. Dis. **34**:201, 1950.
5. Shafer, J. K., Usilton, L. J., and Gleeson, G. A.: Untreated Syphilis in the Male Negro. A Prospective Study of the Effect on Life Expectancy, Milbank Mem. Fund Quart., July, 1954, and Pub. Health Rep. **69**:684, 1954.
6. Schuman, S. H., Olansky, S., Peters, J. J., and Smith, C. A.: Untreated Syphilis in the Male Negro. Background and Current Status of Patients in the Tuskegee Study. (To be published.)
7. Olansky, S., Schuman, S. H., Rivers, E., and Shafer, J. K.: Untreated Syphilis in the Male Negro. Twenty Years of Clinical Observation of Untreated Syphilitic and Presumably Nonsyphilitic Groups. (To be published.)
8. Olansky, S., Simpson, L., and Schuman, S. H.: Untreated Syphilis in the Male Negro. Environmental Factors in the Tuskegee Study, Pub. Health Rep. **69**:691, 1954.
9. Rivers, E., Schuman, S. H., Simpson, L., and Olansky, S.: Twenty Years of Follow-up Experience in a Long-Range Medical Study, Pub. Health Rep. **68**:391, 1953.
10. Bruusgaard, E.: Ueber das Schicksal der nicht spezifisch behandelten Luetiker (The Fate of Syphilitics Who Are Not Given Specific Treatment), Arch. Dermat. u. Syph. **157**:309, 1929.
11. Gjestland, T.: The Outcome of Untreated Syphilis. A Follow-up Study of 2,000 Patients Untreated for Early Syphilis. (Preliminary title of report to be published.) World Health Organ.
12. Clark, T.: The Control of Syphilis in Southern Rural Areas, Chicago, 1932, Julius Rosenwald Fund.
13. Rosahn, P. D.: Autopsy Studies in Syphilis, J. Ven. Dis. Inform., Supp. No. 21, 1947.

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THE OVER-ALL PICTURE OF LONG-TERM ILLNESS*

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THE fact that and the extent to which our population is aging are well known and do not require further documentation. This shift involves profound sociologic readjustments and major changes in the kinds of illnesses for which our communities must provide. These changes in the illness problems of society are occurring rapidly and the lack of "fit" between our illness problems and our facilities and services to meet these problems is becoming increasingly acute.

Chronic illness has been broadly defined by the Commission on Chronic Illness as: "all impairments or deviations from normal which have one or more of the following characteristics: are permanent; leave residual disability; are caused by non-reversible pathological alteration; require special training of the patient for rehabilitation; or may be expected to require a long period of supervision, observation, or care."

When the findings of the National Health Survey conducted in 1935-1936 are adjusted to the 1950 population, it is estimated that approximately 28 million persons or one of six in the United States has some known physical or mental impairment. Forty-five per cent of these persons are under age 45, only 21 per cent are over 65.

Most of these 28 million persons with chronic illness are not disabled, nor do they have handicaps that call for specialized facilities or services. If we direct our attention to persons whose condition has disabled them for three months or longer, we find that 5.3 million persons (3.5 per cent of the population) are in this category.[1] This group conforms fairly closely although not precisely to the definition used by the National Conference on Care of the Long-Term Patient: "The term 'long-term patient' includes only those persons suffering from chronic disease or impairment who require a continuous or prolonged period of care, that is, who are likely to need or who have received care for a continuous period of at least 30 days in a general hospital; or care for a continuous period of more than 3 months in another institution or at home, such care to include medical supervision and/or assistance in achieving a higher level of self care and independence."

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Thus we are considering that group of persons who are substantially disabled for a prolonged period. These persons need a broad array of services organized in a fashion that permits their efficient utilization. In its age composition this group is much older than the total group of the chronically ill (Table I, Fig. 1). Of the 5.3 million long-term patients, that is, the disabled group, 2.1 million (40 per cent) are over age 65. About 1.8 million (34 per cent) are in the middle span 45-64 years, and only 1.4 million (27 per cent) are under age 45. Approximately 8 per cent of the total population is 65 or over; yet, this age group accounts for 16 per cent of the 28 million persons with chronic illness and 40 per cent of the 5.3 million who are disabled three months or more.

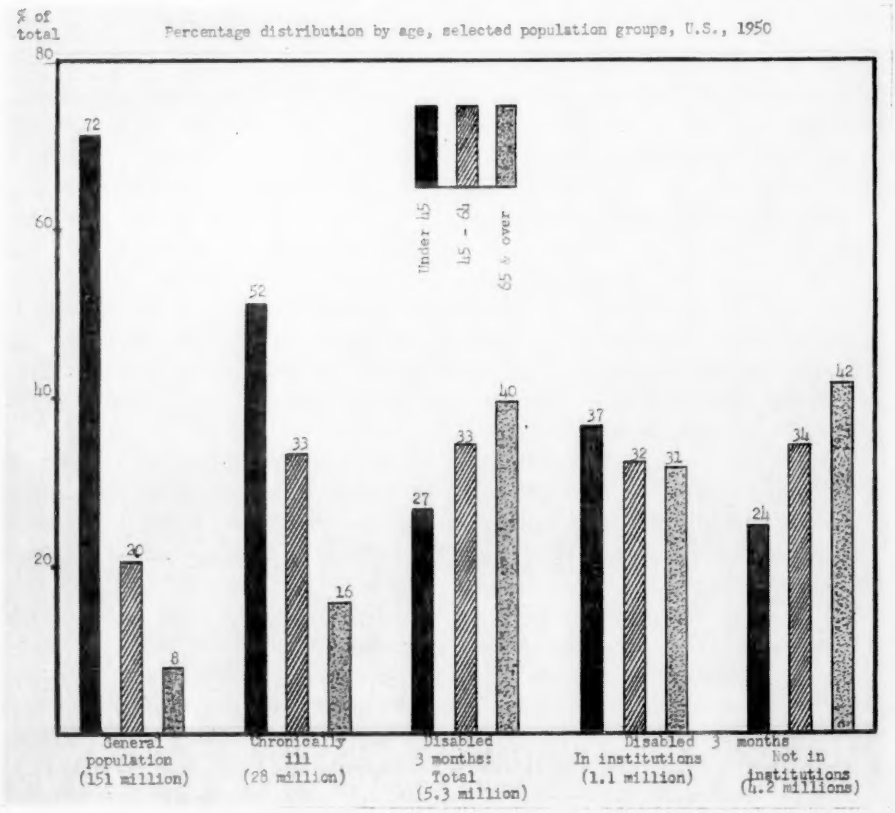

Fig. 1.

Another way of looking at these same facts is in terms of the prevalence of disabling illness for different age groups (Table II). The rate is 1.3 per cent for persons under 45; 5.8 per cent for those between 45 and 64; and 17.1 per cent for those 65 and over. Thus, disabling illness is 13 times as frequent among persons 65 and over as among persons under age 45. This is a matter for serious consideration to a nation whose population is shifting rapidly to a more aged

composition. If we assume that the age-specific prevalence of disabling illness is relatively constant, we can compute the numbers of persons with such illness for 1960 and 1970 as the result of the changes in age distribution of the population. For example, we are assuming that rate of invalidism for persons at a given age, say age 75, does not change materially from decade to decade.

TABLE I. PERCENTAGE DISTRIBUTION BY AGE, SELECTED POPULATION GROUPS, UNITED STATES, 1950

AGE	GENERAL POPULATION	CHRONICALLY ILL	DISABLED 3 MONTHS OR MORE		
			TOTAL	INSTITUTIONALIZED	NONINSTITUTIONALIZED
Number (in millions)	150.7	27.8	5.3	1.1	4.2
PERCENTAGE DISTRIBUTION BY AGE					
Total	100.0	100.0	100.0	100.0	100.0
Under 45	71.5	51.6	26.8	36.6	24.2
45-64	20.3	33.0	33.6	32.0	34.1
65 and over	8.1	15.6	39.6	31.4	41.8

TABLE II. ESTIMATED NUMBER OF PERSONS DISABLED THREE MONTHS OR MORE, UNITED STATES, 1960 AND 1970, BASED ON 1950 RATES OF DISABLEMENT*

AGE GROUP	ESTIMATED NUMBER DISABLED 3 MONTHS OR MORE				
	1950			1960	1970
	NUMBER	% OF POPULATION			
Under 5	55,250	0.34		57,004	58,378
5–14	189,280	0.78		279,295	271,331
15–19	118,430	1.12	1.3	149,890	208,757
20–24	158,650	1.38		155,692	238,726
25–34	395,980	1.67		378,255	416,732
35–44	501,790	2.34		560,383	528,372
45–54	712,020	4.11	5.8	859,319	951,013
55–64	1,069,480	8.04		1,260,752	1,512,887
65 and over	2,097,180	17.09		2,683,301	3,227,447
Total	5,298,060	3.5		6,383,891	7,413,643
Increase over 1950					
Number	XX	XX		1,085,831	2,115,583
Percentage	XX	XX		20.5	39.9

*The method used in developing these data is described in Table I, Source Book on Size and Characteristics of the Problem of Care of the Long-Term Patient (Public Health Service Publication 344), Government Printing Office, 1954.

We have taken the prevalence rate of disabling illness (three months or longer) for each age group, using ten-year intervals, and have applied these rates to the estimated population as projected for 1960 and 1970 by the Bureau of the Census.* It is estimated that the number of disabled persons will increase from 5.3 million in 1950 to 6.4 million in 1960 and 7.4 million in 1970. This represents a 21 per cent increase from 1950 to 1960. Viewing the entire twenty-year span, 1950 to 1970, the increase in the number of disabled persons is 2.1 million persons (40 per cent). In terms of the annual increment of disabled persons, we are adding them to the population at the rate of 106,000 persons, a 2 per cent increase each year.

Let us look more closely at these 5.3 million persons recorded as disabled in 1950. This figure is a composite one and includes:

1. All persons residing in 1950 in hospitals and institutions for long-term care, that is, mental, tuberculosis, and chronic disease hospitals; home and schools for the mentally or physically handicapped; nursing homes and homes for the aged.

2. All persons between ages 15-65 living at home, each of whom reported on household interview "a disabling illness or condition that prevented him (for 3 months or longer) from doing his regular work or carrying out other duties or that allowed him to work only occasionally or not at all."[2]

3. Since the 1949-1950 study by Woolsey[2] excluded children under 15 and adults over age 65, it was necessary to apply data derived from the National Health Survey for these age groups (see footnote, Table II).

Most of this group, 78 per cent, are in the civilian noninstitutional population. They are managing their illness problems in their own home or the homes of relatives with occasional short-term admissions to general hospitals. The extent to which long-term patients are in general hospitals varies in different parts of the country, and national data are not available. A recent unpublished study in Maryland showed that 11.6 per cent of all patients in general hospitals had been there thirty days or longer. If this is representative of the country as a whole, then about 57,000† long-term patients are in general hospitals at any given time. This constitutes slightly over 1 per cent of the nation's 5.3 million long-term patients. Hospitals for long-term care, mental, tuberculosis, and chronic disease account for another 14 per cent, and the remaining 7 per cent are in homes and schools for the mentally or physically handicapped and facilities for the aged and dependent. The important point here is that the greatest number of long-term patients, 78 per cent, are cared for in their own homes and only 22 per cent are in institutions for long-term care. Nevertheless, this 22 per cent amounts to 1,101,651 persons and represents the hard core of the most seriously disabled group for whom care must be provided. The mental hospitals account for over one-half this group (56 per cent). The next largest group of

*Bureau of the Census, Bulletin P. 25, No. 78. The estimates assume: continuation of the decline in age-specific mortality rates observed during the 1940's; and a decline in fertility rates to approximately those of 1939-1940.

†This represents 11.6 per cent of 477,272 (average census of patients in general hospitals registered by A.M.A. in 1953—Hospital Service in the United States, J.A.M.A. **155**:255 [May 15] 1954).

patients is made up of those in nursing homes and homes for the aged, an estimated 235,460 patients (21 per cent). Tuberculosis hospitals account for 7 per cent, and homes and schools for the physically or mentally handicapped 14 per cent. The smallest category, in chronic disease hospitals, accounts for only 20,084 patients, less than 2 per cent of the total (Table III).

TABLE III. PERCENTAGE DISTRIBUTION OF PATIENTS IN LONG-TERM CARE INSTITUTIONS (EXCEPT CORRECTIONAL), BY AGE, UNITED STATES, 1950[1]

AGE	TOTAL	MENTAL HOSPITALS	TUBERCULOSIS HOSPITALS	CHRONIC DISEASE HOSPITALS	HOMES AND SCHOOLS FOR THE HANDICAPPED	NURSING HOMES AND HOMES FOR THE AGED
Number of patients	1,100,651	613,628	76,291	20,084	155,188	235,460
% distribution by type of institution	100.0	55.8	6.9	1.8	14.1	21.4
PERCENTAGE DISTRIBUTION BY AGE						
Total	100.0	100.0	100.0	100.0	100.0	100.0
Under 45	36.6	35.8	62.4	22.9	84.4	0.1
45–64	32.0	41.2	29.0	33.0	12.8	21.4
65 and over	31.4	23.0	8.6	44.1	2.8	78.5

If we examine the age distribution of persons in institutions, we find that those individuals 65 or over account for 23 per cent of those in mental hospitals, 9 per cent of those in tuberculosis hospitals, 44 per cent of those in chronic disease hospitals, and 78 per cent of those in nursing homes and homes for the aged.

If we project the 1950 age-specific prevalence of institutional care against population estimates for 1960 and 1970, the results are interesting and startling (Table IV). Again, it is assumed that the pattern remains essentially unchanged for specific age groups during the period, that is, that a person at age 65 with a stated kind and degree of mental illness is equally as likely to be hospitalized in 1970 as in 1950. These calculations point to a likelihood that there will be 105,000 more persons in mental hospitals in 1960 than in 1950 and that by 1970 the number will increase by an additional 98,000, an over-all increase of 33 per cent.

If we examine the similar changes in relationship to nursing homes and homes for the aged, the result is even more striking (Table V). By 1960 the number of patients in these facilities will have increased by 73,000 (31 per cent), and by 1970 there will be added another 66,000 patients, an over-all increase of 59 per cent in twenty years.

We do not have corresponding national data on the age distribution of patients in general hospitals. However, unpublished studies carried out by the

Commission on Chronic Illness in Maryland show that utilization of the general hospital varies widely with age (Table VI). If the number of patients in general hospitals per 10,000 general population in each age group is expressed as an index (Table VI), the range of this index of hospital utilization is from 32 for persons aged 5 to 14, to 379 for persons aged 85 and over (12 times as great). The index increases without interruption for each decade after age 14. As the aging of the population progresses, general hospitals can hardly fail to experience

TABLE IV. ESTIMATED NUMBER OF PATIENTS IN MENTAL INSTITUTIONS, 1960 AND 1970, BASED ON 1950 RATES OF INSTITUTIONALIZATION

AGE GROUP	ESTIMATED NUMBER IN MENTAL INSTITUTIONS*			
	1950		1960	1970
	NUMBER (ACTUAL)	% OF POPULATION		
Under 15	3,823	0.01	5,257	5,196
15–24	26,018	0.12	29,598	43,126
25–34	77,731	0.33	74,745	82,348
35–44	111,740	0.52	124,530	117,416
45–54	127,292	0.73	152,628	168,915
55–64	125,678	0.95	148,970	178,762
65–74	86,614	1.03	105,297	123,981
75 and over	54,732	1.41	77,240	96,557
Total	613,628	0.41	718,265	816,301
Increase over 1950				
Number	xx	xx	104,637	202,673
Percentage	xx	xx	17.1	33.0

*Excluding schools and homes for the "mentally handicapped."

TABLE V. ESTIMATED NUMBER OF PATIENTS IN NURSING HOMES AND HOMES FOR THE AGED, 1960 AND 1970, BASED ON 1950 RATES OF INSTITUTIONALIZATION

AGE GROUP	ESTIMATED NUMBER IN NURSING HOMES AND HOMES FOR THE AGED			
	1950		1960	1970
	NUMBER (ACTUAL)	% OF POPULATION		
45–64	50,555	0.16	58,542	67,130
65–74	61,527	0.73	74,628	87,870
75 and over	123,378	3.20	175,296	219,136
Total	235,460	xx	308,466	374,136
Increase over 1950				
Number	xx	xx	73,006	138,676
Percentage	xx	xx	31.0	58.9

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the impact of increasing numbers of aged patients and the differences in services needed by the older group. Hospital planning should take these future changes in the hospital population into account.

TABLE VI. NUMBER OF PATIENTS IN GENERAL HOSPITALS PER 10,000 GENERAL POPULATION, AND INDEX OF THE IN-HOSPITAL RATE, BY AGE, MARYLAND, 1953

AGE GROUP	NUMBER OF PATIENTS PER 10,000 POPULATION	AGE-SPECIFIC INDEX OF IN-HOSPITAL RATE*
Total	21.9	100
Under 1†	44.0	201
1– 4	8.4	38
5–14	6.9	32
15–24	17.3	79
25–34	19.7	90
35–44	21.6	99
45–54	27.9	127
55–64	37.0	169
65–74	48.2	220
75–84	67.5	308
85 and over	83.0	379

*Ratio of number per 10,000 for an age group to the number per 10,000 for the total population.
†Excluding newborn infants.

All these estimates of additional facilities needed are the product of two factors: (1) the natural increase in total population, which is estimated by the Bureau of the Census at 29 per cent from 1950 to 1970; and (2) the effect of the changes in age distribution of the population (Table VII). To compute the increased requirement for facilities resulting from aging alone, it is necessary in each instance to deduct that increment resulting from over-all population growth. When this is done for the period 1950 to 1970, we find that one fourth of the increase in the number of persons disabled is due to aging and three fourths to total population growth. The estimated increase in mental hospital population is only 11 per cent due to aging, the remainder being due to population increase. However, the situation in regard to nursing homes and homes for the aged is quite different. The twenty-year increase in patients is equally divided (50 per cent) between change in age and total population increase.

If these data are applied crudely to the Commonwealth of Massachusetts, assuming that this population is aging and growing at the same rate as for the country as a whole (and I realize that this is not quite the case), it would mean that in that state one would need to construct facilities and find staff for 6,000 additional mental hospital patients by 1970 and for 4,300 more patients in nursing homes or homes for the aged. In so doing one would not have improved the facilities in relationship to the need by one iota. The only accomplishment would be to have kept even with increased need stemming exclusively from population changes. Like Lewis Carroll's Alice we have to run very fast just to stay where we are.

I appear to argue that we are caught in a trap and that our only salvation is to proceed with the construction of large numbers of institutional facilities

of all kinds. May I say at once that in my opinion this is not the case. There are many other factors at work which have been deliberately excluded from consideration up to this point, in order to examine the effect of aging and total population increase, while assuming all other factors to remain constant. There is no reason to believe that the revolutionary medical and surgical advances of the last twenty years may not be matched or exceeded in the years ahead. The current investment in biologic, chemical, and clinical research is at a very high rate and there is reason to anticipate that the unknowns of arteriosclerosis, malignant growth, and mental illness will gradually yield to intensive study and experiment. Nevertheless, it has been wisely said that the most reliable statistic is that "one out of one die." To this, I would like to add an hypothesis which I cannot prove but which seems to me to be reasonable. As we increase longevity by improved medical technology and improved standards of living, we extend the age at which death occurs, but we probably do not as yet significantly alter the duration of the period of partial or complete disability which on the average intervenes before death. At some future date, people may live on the average to be 75; they may also retain good health until a later year than they now do; but is there any reason to expect that in the future they will die more suddenly or with a shorter period of disability? I think not. I suspect that we shall continue to wear out unevenly, with one or another organ crippling the functioning of the whole person long before a vital function is lost. If this be true, then medical advances will not result in fewer people needing care for long-term illness, but instead in progressively older people needing this care.

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TABLE VII. ESTIMATED INCREASE IN NUMBER OF PERSONS DISABLED AND NUMBER IN INSTITUTIONS, 1950 TO 1970: PROPORTION DUE TO POPULATION INCREASE AND TO CHANGE IN AGE DISTRIBUTION

	NUMBER IN 1950	INCREASE, 1950 TO 1970			
		TOTAL	DUE TO POPULATION INCREASE (29.4% OF 1950)	DUE TO CHANGE IN AGE DISTRIBUTION (REMAINDER)	% OF INCREASE DUE TO CHANGE IN AGE DISTRIBUTION
Persons disabled 3 months or more	5,298,060	2,115,583	1,557,630	557,953	26.4
Persons in mental hospitals	613,628	202,673	180,407	22,266	11.0
Persons in nursing homes and homes for the aged	235,460	138,676	69,225	69,451	50.1

Concurrent with the aging of the population there are other sociologic changes that aggravate the problem of care of invalids in their own homes. With the phenomenon of industrialization, there has been a movement of families from rural areas to cities. With increasing building costs, there has been a progressive reduction in the size of homes. Children in their twenties tend to move from the family home to distant cities or states; and the new homes they establish are rarely set up to accommodate an invalid parent or relative. The young couple places great importance on independence and freedom from inter-

ference by others. The wife is more likely to be employed than a generation ago. Our cultural pattern is moving perceptibly from the three-generation to the two-generation household. The average size of the household has decreased in each decade during the last sixty years with an over-all reduction from 4.9 per household in 1890 to 3.5 in 1950. As a result, the emotional strain and physical burden of an invalid in the home must be absorbed within a smaller group of persons. If the wife works, there is likely to be no one available to look after the patient. The modern cultural pattern permits the family to escape the responsibilities customary in the past.

What, then, is a constructive approach to this complex problem? Unfortunately there is no simple solution. Rather, there are many limited approaches which in the aggregate may ameliorate, although not solve in any final sense, the problem of long-term care. One serious obstacle to progress is the fact that chronic illness is everyone's problem and, by the same token, no one's clear responsibility. Hospitals, physicians, welfare agencies, health departments, councils of social agencies, community chests—all are deeply concerned and involved, but none is clearly responsible for charting and pursuing a course of action. If a city has an inadequate junior high school there is no doubt in the mind of the citizen as to where the responsibility for correction rests. Likewise, if diphtheria goes uncontrolled the public knows who is failing in his duty. Not so with care of the long-term patient. If the over-all facilities of a community for care of this group are inadequate, if there are overlapping areas, gaps, conflicting administrative policies of different agencies, and the type of general confusion that seems to be all too common, neither government nor the general public can with clarity and firmness say to a legally authorized unit: "This is your problem; it is up to you to chart a course of action that will result in reasonable service for families who have encountered disabling chronic illness."

The nightmare of endless construction of custodial facilities would place a heavy burden of expense on a population already resentful of its tax burden. It also would be a great injustice to many partially disabled persons who have no real need for institutional care. Our institutions now house many patients who could have remained at home but for the lack of some single service—an orthopedic bed for the fracture patient; someone to give a mercurial diuretic to a cardiac patient; someone to lift a heavy paralytic in and out of bed occasionally; someone to shop for the arthritic housewife. The story is repeated over and over: as soon as one important need of the patient develops that the family cannot meet, the patient is placed in a nursing home or some other custodial facility. Once the admission occurs, particularly if the patient is a public charge, the spot in the home from which he came closes over and disappears, and the social worker who later attempts a return of the patient to his home finds that there have been home readjustments and there is no longer any place for the patient.

One of the most constructive steps a community can take is to provide a generous measure of services which will enable families to care for their members at home. Each community will need to determine for itself what services should be offered and by whom. The most frequent and perhaps the most important

is the visiting nurse, offering bedside care whether under public or private auspices. Other important home services would include social case work, physical therapy, the loan of wheel chairs, hospital beds, rubber sheets, homemaker service, friendly visitors. These services may or may not be integrated into a fully organized home care program, but if the services are easily available, if administrative obstacles to their use can be removed through skillful community organization, and if practitioners of medicine are fully informed about these services and will in fact make full use of them, then the community can make substantial progress in preventing unnecessary and unwise institutionalization.

Another of our current failures is the failure to apply the technical knowledge of medical rehabilitation that is now available. Through neglect of these skills, we are literally creating disabilities that need not exist. It is still commonplace for the hemiplegic to be discharged from the general hospital without any retraining as soon as the acute medical crisis is passed. His deterioration may progress quite rapidly to the helpless bedridden invalid with incontinence, contractures, and bedsores in spite of the fact that we know that with proper early rehabilitative care many of these patients can learn again to walk, to control their body functions, and to lead a fairly normal and productive life. Many other examples of this kind could be cited. We are dogged by a highly prevalent defeatist attitude toward serious illness in the older person and a general resistance to the philosophy of rehabilitation. True, there is also a shortage of rehabilitation staff and facilities, but the more difficult obstacle is the lack of interest among hospitals and many professional people in the tedious task of medical rehabilitation. There is also an unwillingness to accept the concept of an interdisciplinary team working jointly toward rehabilitation.

Finally there is the problem of money. This is the single important obstacle to good care for the long-term patient. Sometimes we indulge in pious complaints that the general hospital refuses to admit the long-term patient or, once he is admitted, proceeds to get rid of him as soon as possible. Or we decry the disinterest of the hospital administrator in construction of a wing for the chronically ill in spite of obvious community need. We also belabor the nursing home for its many inadequacies. We either forget or ignore one thing: As a group, long-term patients are not financed. They are not financed on any adequate basis by resources from personal income; prolonged care is excluded from almost all insurance coverage; and government programs for the indigent are circumscribed by the philosophy of providing minimum subsistence and care rather than reconstruction of the health of the person.

The voluntary general hospital cannot be expected to build and operate facilities for these patients as long as no one has evolved a plan through which the cost of these services can be regularly and systematically met. The public has no right to complain about the type of care given in nursing homes as long as most of our welfare departments are purchasing that care at rates ranging from $2 to $3 per day, rates at which it is clearly impossible to provide adequate service.

Fortunately there is evidence that some improvement is taking place. Welfare payments for nursing care are slowly increasing; some states are subsidizing

general hospitals for care of the chronically ill, or are building separate chronic disease hospitals; and a few insurance companies, including Blue Cross and Blue Shield in Massachusetts, are experimenting with coverage of prolonged care and coverage of a wide range of services rendered to the patient at home. These developments are encouraging but up to now they represent only a nibbling at the edge of the large problem of financing long-term care. The present unsatisfactory situation will continue until the public conscience no longer tolerates second-class service for this sizable group of patients, and is willing, through some systematic device or devices, to foot the bill for proper care. The most hopeful approach would seem to be an extension of voluntary, prepayment insurance—covering prolonged as well as brief illness and providing services in the home as well as in hospitals. For those unable to pay the necessary premiums there seems to be no alternative to the basic proposition that society as a whole must pay the bill through taxation.

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REFERENCES

1. Source Book on Size and Characteristics of the Problem of Care of the Long-Term Patient, Public Health Service Publication 344, Government Printing Office.
2. Woolsey, T. D.: Estimates of Disabling Illness Prevalence in the United States, based on the Current Population Surveys of February 1949 and September 1950, Public Health Monograph No. 4, Public Health Service Publication No. 181, Washington, 1952, Government Printing Office, 16 pp.

MEDICAL MANAGEMENT OF THE LONG-TERM RESPIRATOR PATIENT

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EACH epidemic of poliomyelitis leaves in its wake a large number of disabled individuals. As Krusen[1] has said, "Every time the use of a tracheotomy or a respirator preserves the life of an extensively paralyzed child during the acute phase of poliomyelitis, physicians have triumphed over death, but they have created for themselves a problem in chronic illness and in providing facilities for the physical, mental and social rehabilitation of a seriously disabled patient."

We wish to discuss problems in the medical management of some of the long-term respirator patients.

The impaired respiratory capacity of these patients stems primarily from the involvement of primary and accessory muscles of respiration. The diaphragm is the most important respiratory muscle. At rest it accounts for approximately 60 per cent of the ventilation. It secures its innervation, however, from cervical roots III and IV, and occasionally from V. The cervical innervation largely supplies the central portion or central tendon of the diaphragm and its crura. The costal portion of the diaphragm, on the other hand, is largely supplied by the lower six intercostal nerves, which also send some fibers to the central tendon. The intercostal nerves also innervate the intercostal muscles, which also play an important role in respiration. The most important group of accessory muscles of respiration are those of the neck and shoulder girdle, which are chiefly involved in upper costal respiration. A second important muscular structure concerned with respiration is the abdominal wall. All these groups of muscles derive their innervation from the cervical or thoracic segments of the spinal cord. For this reason these long-term respirator cases are primarily those with high spinal involvement. True, of course, some may have had some degree of bulbar involvement during their acute illness; however, there is little evidence that the bulbar residual involvement is the primary source of the long-term respiratory difficulty.

Of the thirty-six patients all except three developed poliomyelitis over eighteen months ago. All of them required the assistance of a respiratory aid

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when they were admitted. Some of these patients had been chronic respirator patients for as long as three years. The vital capacity of most of these patients has varied from a low of 150 c.c. to a maximum of about 900 c.c. on admission. Five have had indwelling tracheotomy tubes since the onset of their illness. The majority of the patients are adults, but their ages range from 2 years to 49 years. All of them also have extensive involvement of the extremities. In fourteen of these, the involvement is so severe that the only muscles which they can control are those of the face and the neck. They are quadriplegics in every sense of the word. As will be noted in Fig. 1, these patients are best grouped together in wards, irrespective of the type of respiratory aid needed. Thus, the patients are kept conscious of the weaning process and the progress they may be expected to make. This does much to improve their morale.

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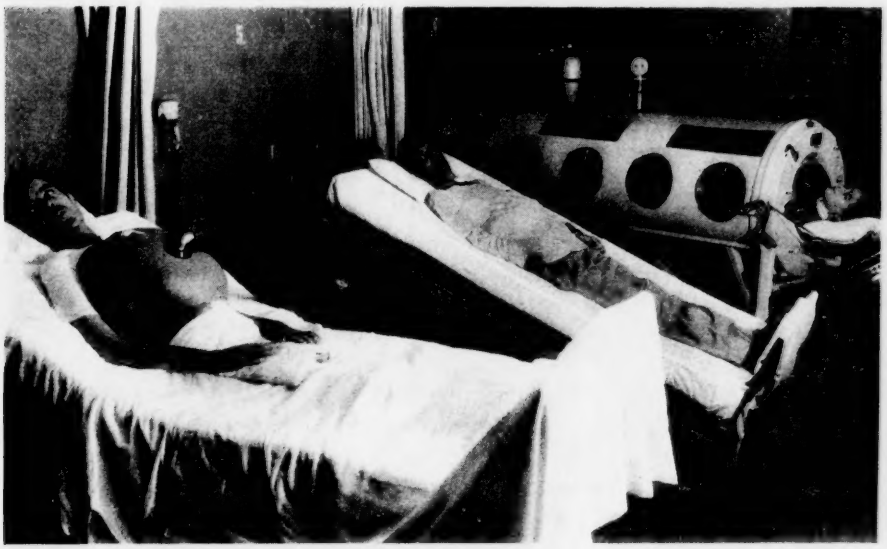

Fig. 1.—Grouping of respirator patients in the ward.

First let us consider the nutritional problem. All of these patients are thin because they have lost a considerable amount of muscle mass. Furthermore, there have been metabolic changes resulting from the prolonged immobilization. Undoubtedly, most of them are in some degree of negative nitrogen balance, although definitive studies have not been made in that direction. It is surprising to note, however, that protein levels are normal in most of these patients, and after the initial period of adjustment to the Center, in which their appetites are very poor, they usually develop good eating habits and eat what might be considered a satisfactory amount for an average person. It goes without saying that meal time in the Center is a difficult one because seven of these patients must be fed, as they are unable to do this for themselves. We have solved this problem largely by the utilization of volunteer groups who come in to assist us at that particular time. We use the usual vitamin supplements and in some

instances we have employed testosterone for its anabolic effect. We are not impressed by the importance of special diets.

The second group of problems is related to the medical picture of the chronic respiratory invalid. First, there are the physical findings. Except for the usual findings in the chest associated with a minimal amount of ventilation and the extensive neurological residuals, physical examination does not reveal much of significance. We are impressed by the frequency with which we see hypertension in some of these patients. It is difficult to interpret this observation, although it does appear more often than would appear to be normal for a population group similar to this one. It has been suggested that in the bulbar involvement of some patients there has been a disturbance in the autonomic centers in the hypothalamus or at least a disturbance in the autonomic pathways as they go through the reticular structure of the medulla. This will bear further study as experience is accumulated. Certainly their hypertension does not appear to respond to the therapeutic agents that we have utilized.

Second, in the laboratory procedures, routine blood counts and urinalyses are performed. Usually these have been of no particular significance. In addition, weekly vital capacities are recorded and tidal air or minute volume studies are noted regularly as different respiratory aids are employed. The Wood modification of the Millikan oximeter is employed to determine arterial saturation of the blood. We have found it very useful in observing how long the patient can tolerate unassisted time without significantly impairing the oxygen arterial saturation of his blood. These findings should be checked at regular intervals with arterial samples of blood examined by the Van Slyke method.

Instead of CO_2-combining power, we prefer to use the pH and the carbon dioxide content as well as the carbon dioxide tension as a more accurate estimation of the degree to which the carbon dioxide is being ventilated out of the lungs.[2] One disadvantage we see at the present time is that it requires too frequent arterial punctures, which are painful for the patient and which reflect only the status of the carbon dioxide in the blood at the time they are made. At present we are also utilizing the infrared gas analyzer (Fig. 2) by which samplings can be quickly taken of alveolar air. These readings correlate closely with the pCO_2 of the blood. While this is not as accurate as the arterial samples, as Collier and Affeldt have shown,[3] the deviation is relatively small and certainly permits one to detect more quickly whether or not the patient is in respiratory acidosis or is maintaining a state of respiratory alkalosis. Our observations on patients to date confirm those of others that these patients have frequently become addicted to a state of respiratory alkalosis and only by careful checking can one give them the required "weaning" that is needed.[4]

Oxygen therapy, of course, is indicated when oxygen lack exists. However, an oxygen tent or a mask is of little use if the patient's hypoxic state is secondary to an obstructed airway. Treatment to increase the CO_2 excretion is simple: an adequate airway must be established, and adequate respiration must be accomplished.

The five patients who have tracheotomies have them plugged, but we are reluctant to discard them because of the need to suction such patients frequently in order to clear the airway. A plastic replica of the inner tracheotomy tube can be used, since it results in much less mucus by being less irritating. Although we have not seen it in our patients, it has been noted by other centers that occasionally a small adenoma may develop in the trachea at the site of the tracheotomy tube, and one death has been reported from obstruction caused by such an adenoma.

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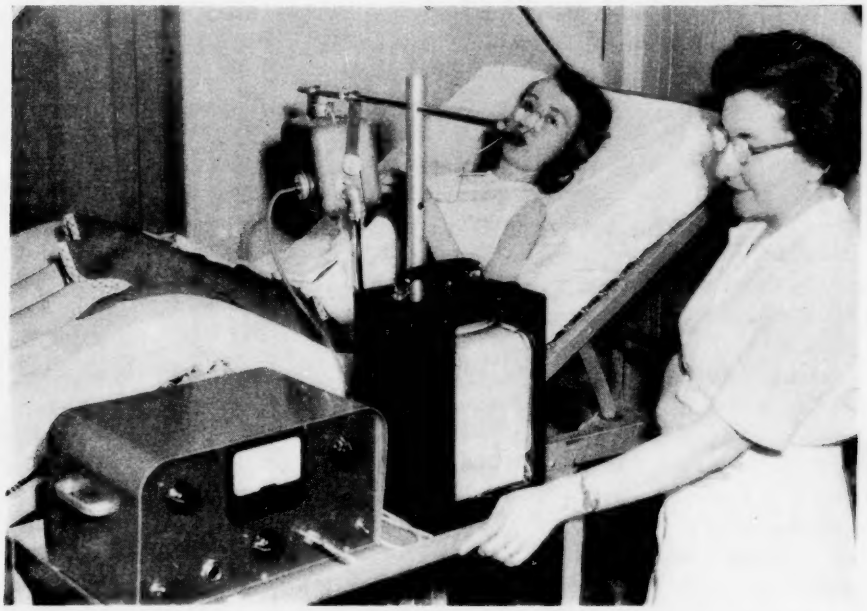

Fig. 2.—Infrared-gas analyzer for rapid samplings of alveolar air.

The most common medical complication we have seen has been that of respiratory infection. This has a way of developing without much evidence other than that the patient has an increased amount of mucus and a poor appetite. The temperature rise is very slight in comparison to the amount of infection. Our usual procedure is to institute promptly a routine in which the patient is given nebulized Alevaire, a detergent aerosol.[5] This may be done conveniently through a tracheotomy tube or with an oxygen tent. If the infection is fairly severe, the Alevaire treatment is continued for twelve to twenty-four hours. With many of the lesser respiratory infections, it is sufficient to give treatments for four hours per day. Frequent suctioning of the patient plus the use of adequate broad-spectrum antibiotics has resulted in the satisfactory control of the respiratory infections in most patients. In only one has there been a major atelectasis. In this particular patient, repeated bronchoscopic aspiration has been utilized; in him, the frequency of upper respiratory infections has increased because of the large atelectatic area.

The diaphragm and abdominal muscles are vital structures in the cough mechanism and all of these patients do not have the normal ability to cough. A mechanical coughing apparatus is available. This apparatus depends upon distention of the lungs with at least 40 mm. of mercury pressure, and then when the pressure is suddenly released, the elastic recoil of the lungs and thoracic wall produces a swift flow of air through the respiratory passages. There is an abrupt expiration that simulates the expulsive blast of the cough.

Recently we have used the exsufflator for the early management of infections according to the method advised by Barach and Beck.[6] We have been impressed by the beneficial effects it has in enabling such patients to rid themselves of the mucus plugs. We think it is most effective when its use is preceded by the administration of an aerosol antibiotic and Alevaire.

What measures are employed to increase respiratory capacities and how successful are they? Since the diaphragm is under the control of skeletal nerves, as also are the accessory muscles of respiration, it is very important that a voluntary effort on the part of the patient be made to strengthen these muscles in the same manner as the impaired muscles of an extremity are strengthened. A fundamental problem in the long-term respirator patient is that the disuse of these muscles results in an immobility so that the weakened muscles are unable to move the more fixed structures such as the thoracic cage or depress the visceral contents.

Thus, the first step consists in getting the patient as often as possible to make an actual effort to breathe more deeply. The nursing staff is a great help in this matter. This is best illustrated by the patient whose tidal volume when measured by the ventilation meter is an average of 300 to 400 c.c. When asked to take deep breaths, not infrequently he can raise that tidal volume to 750 c.c. It must be recognized, however, that maximal breathing capacity is tremendously impaired and although a few tidal volumes could be greatly increased, fatigue would not permit the patient to continue this for a long period of time. For this reason, we observe the minute volume. If the patient is to develop his weakened muscles, he must periodically make a greater attempt to utilize his own muscles with less respiratory aid.

This is accomplished by the progressive weaning program in which a certain portion of time is devoted to the tank respirator, another portion to the chest respirator, and another portion to the rocking bed, and subsequently another portion to unassisted time. Thus, the patient has spent throughout the twenty-four hours a certain amount of time with each type of respiratory aid. The ultimate goal of such a program is to increase the unassisted breathing time of the patient and to lessen the respiratory aids given the patient. The change from one respiratory aid to another, and finally to unassisted time, must be made gradually and under good clinical control so that the patient is not getting himself into a state of respiratory acidosis.

We wish to cite a typical case.

L. B., a 15-year-old white boy, contracted acute poliomyelitis on Aug. 26, 1952. Within forty-eight hours after onset, he had developed respiratory paralysis and was placed in a tank respirator. He remained in this continuously for sixty days and then a gradual weaning process

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was begun. On July 13, 1953, he was admitted to our Center. At the time of admission he had a complete flaccid paralysis of the upper extremities, with generalized weakness of the lower extremities. The respiratory muscles were paralyzed to such a degree that he had a vital capacity of 250 c.c. and required continuous respiratory aid. On June 22, 1954, his vital capacity had been increased to 745 c.c., his minute volume was 5,400 c.c., and his tidal volume was 325 c.c. Arterial oxygen saturation studies, as well as pCO_2 measurements, remained within normal limits even after periods of eight to ten hours without any assistance. There has been no return of function in his upper extremities, but there has been an increase in function of his lower extremities. He is now able to walk and has developed considerable dexterity with his feet, which permits him many activities. There is every evidence that his progress will continue. Fig. 3 illustrates the record of patient L. B. and his progressive weaning from the tank respirator.

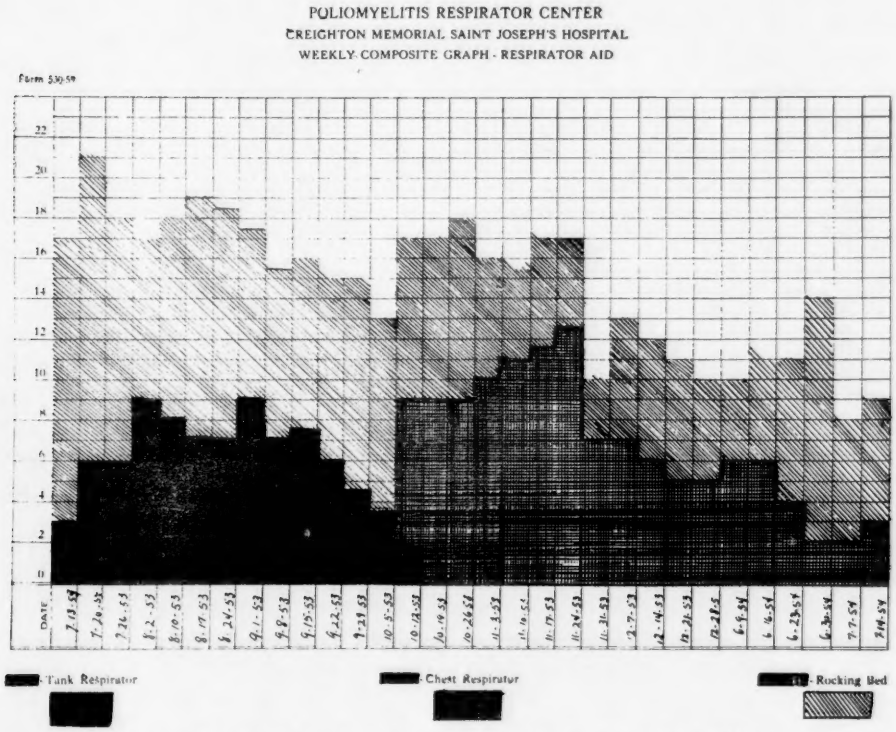

Fig. 3.—The gradual weaning of a paralyzed patient from the tank respirator.

The second step in aiding the patient is to "unfreeze" the thorax,[7] since most of the patients whom we have received do have what might be considered a frozen thorax. A number of methods are employed to do this. Positive pressure inflation of the lungs several times daily may help keep the thorax flexible. If the patient is utilizing the tank respirator, one can use the deep-breathing device, which consists of periodic negative pressures of 35 or 40 cm. of water. Positive pressure may have some disadvantage in that there is impairment of the venous return of blood to the heart. The use of blow bottles and balloons has long been advocated; these are of questionable value. Physical

therapy measures are also employed, which consist of chest compression, individual massage, and stretching the intercostal muscles. Attempts are made to increase the tone and power of the neck muscles and thus give them greater power to elevate the thoracic cage as a method of keeping the thorax flexible. The ability to hyperextend the head at the time of inspiration will also increase vital capacity.

In order to demonstrate their effectiveness, we have been using coarse measurements of compliance which involve determining the degree of negative respirator pressure required to give varying tidal volumes.[8] If the negative pressure which is required to produce a given tidal volume lessens over a period of time, this should be relative evidence that the total compliance at least has not become worse. A number of the progress charts of patients in the Center demonstrate that there has been made a progressive improvement in their capacity to respirate. Although it is surprising how well a chronic respirator patient can do with a vital capacity of 500 or 600 c.c., it is our policy not to require patients to go unassisted any significant time until they have a vital capacity of at least 25 to 30 per cent of their predicted values. These patients, in the presence of a respiratory infection, must of course have some respiratory aid.

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There is a considerable difference between the amount of progress that some patients can make. Some cannot significantly increase their vital capacity over a considerable period of time, although we have been able to help them to get along comfortably with much less respiratory aid. This should emphasize that the employment of the vital capacity alone as a measurement of progress is unsatisfactory. We have tried to teach some of our patients the "frog breathing" or glossopharyngeal breathing described by Dail in California.[9] Eight of our patients have learned it quite readily. It is valuable in that it gives the patient some additional reserve which he can utilize in the presence of failure of his respiratory aid. It also enables him to talk louder, and perhaps due to the sudden release of expiratory pressure, it assists in bronchial drainage and in coughing. One patient who has a vital capacity of 750 c.c. can increase it to 2,400 c.c. by this method. This helps to keep the thorax flexible; it is fatiguing and it requires adequate strength and normal function of the tongue, cheek, mouth, soft palate, larynx, and pharynx.

While a logical goal for respirator patients would be to have them breathe unassisted, yet we must recognize that in approximately 15 per cent this will not be possible. Therefore, our goal, as in other centers, is to bring the patient to such a state that he can go home with some respiratory aid. Usually this will consist of a portable chest respirator and a rocking bed. A patient using such devices needs but one attendant for his care, whereas a patient in a tank respirator requires two or more people. The return to the home situation is a very worth-while goal in view of the tremendous cost involved in hospitalization. Prior to the time of the patient's discharge, an attendant is procured and trained at the Center. The attendant is instructed in regard to the use of the respiratory aid. Instruction is also given in regard to the regimen of physical therapy and occupational therapy which is to be continued at home. At regular intervals

the patient is returned to the Center for continued follow-up. In the presence of acute respiratory infection, the patient is admitted as an emergency, for vital capacity is markedly reduced with pulmonary infections.

One advantage of a center such as this is that it develops more completely a team approach to this chronic disease problem, and provides a pool of trained personnel who, by cooperation, can secure better results.

The psychologic factors and rehabilitation needs that play a vital part in the care of these patients will be the subject of another paper. Since medical science has created this dilemma of the chronic respirator patient, it also must find the answer to the more efficient care of such patients.

REFERENCES

1. Krusen, F. H.: Physical Medicine and Rehabilitation for the Chronically Ill, J. Am. Geriat. Soc. **2**:75, 1954.
2. Comroe, J. H.: Methods in Medical Research, vol. 2, Chicago, 1950, The Year Book Publishers, Inc.
3. Collier, C. R., and Affeldt, J. E.: Chronic Hyperventilation in Respirator Patients. (To be published.)
4. Affeldt, J. E.: Personal communication.
5. Ravenel, F. F.: New Technique of Humidification in Pediatrics, J.A.M.A. **151**:707, 1953.
6. Barach, A. L., Beck, G. J., Bickerman, H. A., and Seanar, H. E.: Physical Methods Simulating Cough Mechanisms, J.A.M.A. **150**:1380, 1952.
7. Waring, J. J.: The Chronic Pulmonary Invalid After Poliomyelitis, Am. J. Phys. Med. **31**:252, 1952.
8. Wittenberger, J. L., and Farris, B. G.: Respiratory Function in Poliomyelitis, Am. J. Phys. Med. **31**:226, 1952.
9. Dail, C. W.: Glosso-pharyngeal Breathing by Paralyzed Patients, A Preliminary Report, California Med. **75**:217, 1951.

Review

RHEUMATOID ARTHRITIS: A REVIEW OF RECENT ADVANCES IN OUR KNOWLEDGE CONCERNING PATHOLOGY, DIAGNOSIS, AND TREATMENT

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INTRODUCTION

THE past seven years have witnessed a remarkable expansion and intensification of activities in clinical investigations and laboratory research on many of the rheumatic diseases, especially rheumatoid arthritis. As a result, new knowledge has been gained and old concepts revised or abandoned. In the review which follows no attempt has been made to cover exhaustively all the recent literature on rheumatoid arthritis. The discussion will focus on the three aspects of this disease with which the authors have had direct experience: pathology, serologic diagnosis, and treatment.

I. PATHOLOGY OF RHEUMATOID ARTHRITIS

The diagnosis of rheumatoid arthritis rests upon the demonstration of idiopathic, chronic inflammation in multiple, diarthrodial joints. Few, if any, of the individual pathologic changes can be said to have an absolute degree of specificity. As a result several patterns of chronic, deforming arthritis are subject to different interpretations. Ankylosing spondylitis, for example, is not regarded as a manifestation of rheumatoid arthritis in most European clinics. As will be pointed out, there are fundamental, pathologic similarities between the two entities. It is argued by some that the histologic changes are so nonspecific as to offer little positive support to the thesis of the identity of the two disorders. A problem of similar difficulty exists when changes of this sort occur in only one joint. Except in instances where the diagnosis of monarticular rheumatoid arthritis is confirmed by subsidiary (for example, serologic) tests, there may be no histologic basis for determining the etiology with certainty. Furthermore, extra-articular changes occur in varying incidence in patients with

rheumatoid arthritis. Since none of these is pathognomonic of rheumatoid arthritis, a question arises as to the significance of their association with the arthritis. The significance must be evaluated in each instance.

When recognition is made of these limitations, the composite pattern is revealed to be fairly characteristic. It follows that biopsy may be a useful tool in establishing the diagnosis of rheumatoid arthritis. This is particularly true in the case of the synovial membrane and subcutaneous nodule.

A. *Joint Structures.*—

1. *The synovial membrane*: The earliest changes are recognized in the synovial membrane that lines the articular cavities. The vessels are congested and the surrounding tissue edematous. Diapedesis of polymorphonuclear leukocytes from the superficial vessels takes place. The lining synovial cells swell, proliferate, and some become desquamated. Fibrin exudes from the capillaries into the fluid at the same time and coagulates onto the denuded synovial surfaces. These changes are reflected in the development of an effusion that contains fibrin, many polymorphonuclear leukocytes, and desquamated synovial cells. Early there occurs a rich proliferation of capillaries from the pre-existing vessels in the superficial portions of the synovial membrane. This is accompanied by a proliferation of fibroblasts. Chronic inflammatory cells infiltrate the internal portions of the membrane in progressively increasing numbers. Lymphocytes predominate but there may be a large proportion of mononuclear cells and, later, plasma cells. Frequently these cells form compact aggregates that superficially resemble lymphoid follicles. At times, multinucleated giant cells appear near the synovial surface. Minute areas of hemorrhage and hemosiderosis are encountered frequently.

As a result of the proliferation and infiltration, the synovial membrane becomes thickened. The thickening takes the form of a papillary or villous hypertrophy. It may be of great proportion; for example, an area that is normally 1 to 2 mm. thick may increase to 10 to 15 mm. As a result, the joint space may be widened sufficiently to be recognized on the roentgenogram.

Special comment should be made about an additional component of the histologic picture, the so-called "fibrinoid" change. This term refers to apparent alterations in the collagenous tissue whereby it assumes close morphologic similarities to fibrin. Although commonly described in the subcutaneous nodule of rheumatoid arthritis and some other rheumatic lesions, we have observed a pattern of "fibrinoid" change with considerable frequency in the more florid stages of rheumatoid synovitis as well. Several types of "fibrinoid" change may be distinguished histologically in rheumatic and other disorders. In the present instance, it is characterized by a swollen, hyaline appearance of the fiber bundles. The coarse bundles are composed of compact masses of delicate fibrils that lack the uniform arrangement of normal collagenous tissue. Instead of being parallel to each other, the fibrils are disheveled to a varying degree. The fibrils enmesh each other so that the bundles become fused in large part. The fibrils are eosinophilic and react as fibrin does with phosphotungstic acid-hematoxylin stain. In van Gieson preparations, they lack the affinity for fuchsin

that normal collagen has. The great majority are not argyrophilic. They possess a degree of anisotropism comparable to that of fibrin or loose connective tissue. In itself, such "fibrinoid" change is not pathognomonic of rheumatoid arthritis. The pattern of the change, however, is quite characteristic in rheumatoid synovitis. Between the bundles are clear spaces in which distorted fibroblasts or synovial cells are dispersed. The cells are discrete. Ordinarily they are elongated and lie parallel to the margin of the bundles. A small proportion are multinucleated. The cells are quite similar to those seen in the subcutaneous nodule, although not usually oriented in a palisade as in the nodule. The areas of "fibrinoid" change usually are located near the surface of the synovial villi. Like fibrin, the "fibrinoid" material may serve as a lattice for the further proliferation of granulation tissue. The intimate association with the exudate of the ulcerated surfaces suggests that the material may actually be fibrin that is undergoing organization and incorporation into the synovial membrane.

In a small proportion of cases, all or part of the synovial lesion resembles the subcutaneous nodule. It is our impression that this "granulomatous" form of synovitis occurs primarily in early and fulminating instances. What relationship the "granulomatous" synovitis bears to the ordinary, nonspecific rheumatoid synovitis is not clear at the present time. Further clarification of this problem will serve to elucidate the histogenic connection between the subcutaneous nodule and the synovial lesion that would otherwise appear to be dissociated. The areas of "fibrinoid" change referred to previously may well represent a bridge between the two. There is an impressive similarity in the appearance of the early subcutaneous nodule and the more acute stages of the synovitis.

It is obvious that more extensive pathologic observations, particularly in the early stages of the disease, are necessary to illuminate these and other problems. Valuable information is obtained by closed, punch biopsy of the synovial membrane of the knee.[1] The procedure is carried out with ease and ordinarily causes little or no discomfort. It is not the custom in this country to perform extensive dissection of the joints at necropsy. This seriously limits our understanding of various rheumatic disorders. To some extent, this difficulty may be overcome by pathologic examination of the sternoclavicular joint of patients who die with this disorder.[2] This articulation is involved in more than one-half the patients. It is readily accessible following ordinary post-mortem routine. There is no cosmetic deformity, and special permission for the procedure is not necessary. Examination of this joint is by no means to be considered a satisfactory substitute for dissection of the articular structures principally involved in rheumatic diseases. Nevertheless it does offer useful material for study when others are not available.

2. *Articular cartilage*: The articular cartilage is relatively resistant to the inflammatory process, but ultimately yields to it. Both on the articular and the subchondral, bony aspect, areas of resorption appear concurrently with replacing granulation tissue. On the articular aspect, the granulation tissue is continuous with that in the synovial lining. There is a corresponding gross

encroachment of the thickened, villous membrane onto the margins of the cartilaginous surface. The layer of granulation tissue that covers the cartilage is firmly adherent to it and is known as pannus. The cartilage ultimately becomes completely replaced by the granulation tissue. Adhesions between opposing villous tufts give rise to ankylosis. Fibrous adhesions may undergo ossific replacement, and bony, as well as fibrous, ankylosis ensues. Extensive subchondral granulation tissue is associated with resorption of the bony trabeculae. This accounts for the rarefaction of bone observed roentgenographically in this location. With subluxation and the resorption of bone, deformity often develops.

3. *Variants of rheumatoid arthritis:* In *ankylosing spondylitis* (Marie-Strümpell), the primary changes take place in the sacroiliac and small, intervertebral (apophyseal), and costovertebral joints. The lesions are of the nonspecific sort observed in the peripheral joints of rheumatoid arthritis.[3,4] This is followed by ossification of the external portions of the annulus fibrosus of the intervertebral discs and also of the paraspinal ligaments. As a result, bony continuity is established between the vertebral bodies with the development of rigid or "poker-back" spine.

The sequence of events in the development of the intervertebral ossification is not well understood. Roentgenographically one may observe areas of dissolution of bone along the margins of the vertebrae prior to the changes in the ligaments and annulus fibrosus.[5] On rare occasions destructive lesions of rheumatoid granulomatous type may be demonstrated pathologically in the vertebral column.[6] Nevertheless, one commonly observes ossific metaplasia in these tissues without residual anatomic evidences of antecedent inflammatory reaction.

In Still's disease, or *juvenile rheumatoid arthritis*, the changes are indistinguishable from the adult disease. There appears to be a greater tendency for the spine to be involved than in the adult form of peripheral arthritis.

In *psoriatic arthropathy*, there are certain pathologic differences from rheumatoid arthritis other than the distribution. Although a severe chronic synovitis with ulceration of the articular cartilage and underlying bone is present, pannus formation is not seen characteristically.[7]

The pathologic alterations of the joints in rheumatoid arthritis are evidence of the action of an inflammatory agent of low grade. They are not at all of a known trophic, endocrine, or other type. They bear no similarities to the lesions observed in the noninflammatory metabolic arthropathies of gout and ochronosis.

B. *The Subcutaneous Nodule.*—

In the early phases of its development, the subcutaneous nodule consists largely of vascular granulation tissue.[8] The large, newly formed capillaries and proliferating fibroblasts lie within edematous subcutaneous tissue. Focal areas of infiltration with chronic inflammatory cells, including a small proportion of eosinophilic leukocytes, are scattered about some of the vessels. In some areas, material resembling fibrin is associated with the fibers about the newly formed or pre-existing vessels. In this vicinity, the connective tissue cells frequently become pleomorphic, occasionally multinucleated. This is the stage that closely

resembles the florid synovial lesion. Necrosis of the tissue takes place where the process is more severe.

The "fibrinoid" material apparently courses along the planes of the collagenous fibers. The cells that lie at the margin of the necrotic areas are oriented in their long axis along these fibers. The majority of the cells are arranged radially with respect to the zone of necrosis for this reason. In this manner, they come to form a "palisade" or closely arranged layer of parallel, elongated cells.

The occurrence of the "fibrinoid" change and necrosis in relation to vessels and the fact that these processes apparently follow the planes of the adjacent connective tissue suggest that a necrosis-producing agent is fluid-borne into the latter from the vessels. The vessels are at times themselves acutely inflamed and necrotic.

The nodules endure in relatively indolent state for many years. As they age, the areas of necrosis become sharply circumscribed by fibrous tissue. There is, as in other types of cicatrizing granulation tissue, a loss of vascularity and progressive hyalinization of the collagenous tissue. A cellular palisade persists between the central detritus and peripheral zone of fibrosis for many years. This is not a static zone, but one where necrosis and cellular proliferation are taking place continually. The necrotic material becomes progressively more amorphous, contains less material resembling fibrin, and accrues large amounts of grumous lipid. As much as 7 per cent of the wet weight of the detritus may be lipid—cholesterol (free and esterified), phospholipid, and neutral fat. Associated lipochrome pigment is responsible for the yellow color observed grossly in the areas of necrosis. The lipid is largely concentrated within the cells of the palisade and located internal to them where necrosis is most recent. Lipase and acid phosphatase activity may be demonstrated histochemically in this region with ease. Extensive calcification is not seen. The end result of the lesion may be an encapsulated, fibrous cyst containing grumous and semifluid material. Occasionally, there is a palisade of cells lining such a cyst that resembles synovial membrane. Not infrequently areas of new nodule formation are present side by side with more quiescent or burned-out ones. There is a striking similarity to the appearance of the subcutaneous nodule of rheumatic fever. This is particularly true in the early phases of the lesion where the extensive fibrosis and large, circumscribed areas of necrosis are not present. Aside from differences in the distribution of the nodules and in their size, one may commonly distinguish between the two on the basis of more extensive necrosis in the rheumatoid lesion. This is observed even in the early phases of its development. Undoubtedly there are instances where this is not true. Furthermore subcutaneous nodules, indistinguishable from those of rheumatic fever or rheumatoid arthritis, are observed on occasion in individuals who do not have other manifestations of either disorder.[9] Subcutaneous nodules are virtually unknown in patients with ankylosing spondylitis. They occur infrequently in juvenile rheumatoid arthritis.

The occurrence of the nodules at sites of pressure suggests that mechanical factors play a role in the development of the lesion. It is striking that the

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granulomatous lesions of rheumatoid arthritis occur primarily in dense connective tissues, subject to mechanical stress or shearing motion—the pressure points over bones, the joints, the roots and leaflets of the valves of the left side of the heart. The streaming character of the zones of necrosis may indicate that mechanical factors affect the form of the nodule as well. The failure of the synovitis to assume the granulomatous form more frequently may reflect the fact that inflammation is not confined within a continuous tissue but may be dissipated into the articular cavity.

C. *Tendons and Bursae.*—The tendons, their sheaths, and bursae are at times involved in pathologic processes similar to those described in the joints. Ball[10] has described fibrinoid necrosis as a primary manifestation of tendon involvement. Granulation tissue forms and undergoes an evolution like that described in the subcutaneous nodule. It has been suggested that healing and cicatrization of such tendonitis contributes to the deformity of the fingers.[10,11]

D. *Heart.*—There exists a fairly extensive literature concerning cardiac changes in rheumatoid arthritis. Much of the interest in this subject has stemmed, on one hand, from a belief in a fundamental relationship of rheumatoid arthritis to rheumatic fever and, on the other, from the clinical observation of acute pericarditis in appreciable numbers of individuals with rheumatoid arthritis. It appears that four pathologic alterations of special significance may be found in the heart[12]:

1. There are ample anatomic evidences of old *pericarditis*, at necropsy, in many rheumatoid patients. In perhaps as many as 25 per cent fibrous pericardial obliteration is found, for which no explanation is present other than the rheumatoid disease. Frankly granulomatous pericarditis is known to occur in rare instances. We may properly speculate that the fibrous pericardial adhesions are evidence of healed rheumatoid pericarditis. The clinical observation of such pericarditis is much less frequent than the pathologic finding. Under circumstances in which pericarditis occurs in association with other abnormalities of the heart, clinical evidences are frequently inconspicuous and evanescent. It is not surprising, therefore, that in rheumatoid arthritis, in which the pericarditis is so frequently an isolated cardiac lesion, its presence may not be recognized clinically.

2. The occurrence of *rheumatic heart disease* has been reported by various pathologists to be high, the incidence ranging from 19 to 66 per cent. It is apparent that much of the disparity between data of various reports is due to differences in the pathologic criteria employed for the diagnosis of rheumatic heart disease and also to factors of statistical bias in the samples being studied.[13] There can be no doubt that the incidence of rheumatic heart disease is much lower than that described in such reports. Nevertheless, it does appear that heart disease, morphologically indistinguishable from the rheumatic type, is found in association with rheumatoid arthritis at necropsy with greater frequency than chance would dictate.

3. Recent years have seen the evolution of a concept of *rheumatoid heart disease*, quite specific to rheumatoid arthritis. This is characterized by granulo-

matous inflammation similar to that of the subcutaneous nodules. Nodular areas of involvement have been seen in the roots and leaflets of the aortic and mitral valves, the adjacent myocardium, and in the epicardium. At times lesions of similar character may be appreciated only microscopically. In the epicardium, the nodules may be accompanied by diffuse, nonspecific chronic pericarditis with or without smaller granulomatous foci. While it is conceivable that healed or minor lesions may lead to deformities indistinguishable from those of rheumatic heart disease, the proof for this is lacking at present. Nodular deformity of the valve may lead to its incompetence. The lesion must be recognized as a rare one, occurring in perhaps 1 per cent of patients with the disease. Bauer and associates[14] have observed aortic insufficiency as a manifestation of ankylosing spondylitis.

4. Small branches of the *coronary arteries* may be involved in an inflammatory reaction similar to that seen in other arteries in patients with rheumatoid arthritis.

E. *Blood Vessels.*—During a study of the striated muscle in rheumatoid arthritis, it was discovered that inflammatory changes are present in small arteries in approximately 10 per cent of biopsy specimens.[15] Although the arteritis does not possess distinctive histologic characteristics, it is believed to be a specific manifestation of the disease because (1) it does not occur in striated muscle in conditions other than rheumatoid arthritis, (2) the histologic features of the inflammatory reaction are fairly constant, and (3) the process is limited to very small arteries. The inflammatory exudate is composed of mononuclear cells. These cells infiltrate the adventitia principally but the media to some extent as well. Necrosis of the wall of the vessel usually is of minor extent, and thrombosis is not present typically. Similar vascular lesions are scattered in other areas—in the nerves,[16] heart,[17] and infrequently in other viscera. They occur in the subcutaneous nodule with special frequency during the early phases of its formation. Indeed the intimate association of the early nodule with the blood vessels suggests that the arteritis may play a special role in the development of the nodule.[8] In the granulomatous lesions, arterioles and capillaries may be involved as well as the arteries. The observation is of importance because it reflects the systemic nature of the disease. It adds another point of similarity to the several known to exist in certain other rheumatic diseases—especially rheumatic fever and systemic lupus erythematosus.

In addition to what may be termed "rheumatoid arteritis," polyarteritis nodosa occurs with conspicuous frequency in rheumatoid arthritis. Polyarteritis nodosa is distinguished from rheumatoid arteritis by its more extensive mural necrosis and widespread visceral distribution. The relationship between polyarteritis nodosa and rheumatoid arteritis is obscure although probably not fortuitous. The polyarteritis nodosa in patients with rheumatoid arthritis is frequently very chronic and has been known to persist as long as fourteen years. We may speculate that the polyarteritis nodosa represents a particularly severe form of rheumatoid arteritis. Some analagous relationship presumably exists between polyarteritis nodosa occasionally observed in rheumatic fever and systemic lupus erythematosus and the vascular lesions of these diseases.

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A number of papers reporting polyarteritis nodosa developing in patients with rheumatoid arthritis while being treated with cortisone,[18-20] corticotropin, or phenylbutazone[21] have appeared recently. The polyarteritis nodosa has been attributed to the medication by some investigators. Others have observed its development in the wake of discontinuing such therapy.[22] Since this vascular disorder is known to occur independently of such therapeutic agents, it is apparent that further controlled observations of the incidence of this complication should be made in order to warrant such conclusions.

F. *Skeletal Muscles.*—In 1945, a distinctive lesion of the striated muscle in rheumatoid arthritis was described by Freund, Steiner, and associates.[23] The lesion is characterized by a focal, compact infiltration of lymphyoctes in and about the muscle. It is widely distributed throughout the muscles. The infiltrate resembles closely the "lymphorrhage" seen in the muscle of myasthenia gravis with the exception that it is closely related to minute vessels—capillaries and sometimes arterioles and venules. The lesion occurs in the majority of patients with rheumatoid arthritis. Nevertheless identical infiltrates occur with considerable frequency in other rheumatic diseases and occasionally in individuals with none of these disorders. For these reasons, the biopsy of striated muscle offers little in establishing the diagnosis of rheumatoid arthritis.[24]

Independent of such myositis, the muscle undergoes nonspecific atrophic changes.

G. *Nervous System.*—

The presence of inflammatory lesions in the peripheral nerves in rheumatoid arthritis also was described by Freund and Steiner.[25] The changes are quite similar to those seen in the muscles. They occur with greater frequency in the larger trunks than in the fine ramifications. Their specificity for rheumatoid arthritis had been challenged since they may be seen in other rheumatic diseases and certain neurological disorders, such as anterior poliomyelitis. Specific alterations of the central nervous system and the sympathetic ganglia have not been found.[26]

H. *Eye.*—

Chronic scleritis of granulomatous type occurs in occasional patients. Although the lesion bears some resemblance to the subcutaneous nodule of rheumatoid arthritis,[27] closely similar forms of scleritis are observed at times in patients who have no evidence of arthritis. As a result of necrosis with softening, defects in the scleral coat may develop and uveal tissue herniate through the sclera or cornea (*scleromalacia perforans*).

Chronic iridocyclitis (uveitis) is observed with some frequency in rheumatoid arthritis, particularly in the juvenile[28] and spondylitic types. So far as is known, the pathologic changes do not have a specific character.[27] *Band-shaped keratopathy* frequently develops secondary to the iridocyclitis. It is characterized by a zone of fibrosis and opacity in the equator of the cornea. Juvenile rheumatoid arthritis is by far the commonest disorder associated with the band-shaped lesion in children.

Sjögren's syndrome is characterized by diminished lacrimation, chronic keratoconjunctivitis, atrophic rhinitis, enlargement of the parotid glands, and frequently rheumatoid arthritis. It appears that the syndrome overlaps with Mikulicz's disease.[29] In both conditions, there is a massive lymphocytic infiltration of the parotid and lacrimal glands associated with atrophy of the parenchymal structures.

I. *Endrocrine Organs.*—

The *adrenal cortex* in rheumatoid arthritis, as in other rheumatic diseases, has no morphologic changes that distinguish it from the cortex in nonrheumatic diseases. It responds in the same manner to the administration of corticotropin and cortisone as it does in nonrheumatic diseases.[30]

Pearse[31] has described a significant degree of degranulation of the "mucoid" (corresponding largely to the basophil) cells of the anterior lobe of the *pituitary gland.* The degranulation was observed only in active cases. Pearse regarded the changes as evidence of a distinct endocrine abnormality. The observation has not been confirmed by Bennett.[32]

J. *Hematopoietic System.*—The state of the *bone marrow* varies with complicating disorders. In uncomplicated periods, it is relatively hyperplastic and the proportion of plasma cells is increased.[33]

The *lymph nodes* become enlarged in a small proportion of cases. Superficial adenopathy, usually in the region of affected joints, is more common than generalized hypertrophy. Microscopically there are nonspecific hyperplastic changes, often with prominent enlargement of germinal centers.[34] The latter may cause confusion with giant follicular lymphadenopathy (Brill-Symmers). The association of lymphadenopathy with leukopenia and splenomegaly is referred to as Felty's syndrome.

The *spleen* is enlarged infrequently. At times, splenomegaly may be attributed to intercurrent disorders, such as amyloidosis or cirrhosis of the liver. In other instances, it may be associated with hypersplenism. The histologic changes are not distinctive.[35] Enlargement is due largely to congestion.

K. *Visceral Granulomata.*—

Aside from the granulomatous manifestations of rheumatoid arthritis in the subcutaneous nodule, synovial membrane, and heart, similar changes may be observed on rare occasions in scattered visceral locations[36,37] such as the splenic capsule, pleural membrane, lung, and kidney. These lesions are quite rare and frequently are less distinctive than those in the previously mentioned sites. Their specific nature is attested to by their association with the other manifestations of rheumatoid arthritis and absence of other assignable causes. It has been suggested that they are especially prone to occur after adrenocortical hormone therapy. As in the instance of polyarteritis nodosa, this must still be regarded as hypothetical.

L. *Complications and Miscellaneous Changes.*—

Secondary amyloidosis is a common complication of rheumatoid arthritis, both of peripheral and spondylitic types.[38,39] It occurs in as many as 20 per

cent of severely incapacitated individuals at necropsy. Amyloidosis is the commonest cause of renal insufficiency in patients with rheumatoid arthritis. It also is responsible for a good proportion of the instances of splenomegaly.

In bedridden patients, *bronchiectasis* and *chronic pneumonitis* are prone to develop. Neither of these nor decubitus ulcers account for the majority of instances of amyloidosis. Infection of the urinary tract with *chronic pyelonephritis* also is likely to occur in such persons.

Despite abnormalities of the albumin-globulin ratio in the serum, hepatic changes are not frequent or specific.[40] It is our impression that chronic *peptic ulcers* are more likely to occur in patients with rheumatoid arthritis than in the general population.

There appears to be some special association of rheumatoid arthritis with chronic *disseminated lupus erythematosus.* It is now clear that a fair number of patients with either of these disorders ultimately develop evidences of the other.[41-44] Positive serologic tests for rheumatoid arthritis (streptococcal or sensitized sheep red-cell agglutination) occur in some patients with lupus erythematosus. At times, "L. E. cells" are demonstrated in patients with well-developed rheumatoid arthritis.[42-46] The visceral lesions of the two disorders overlap to some extent, so far as the cardiovascular tree is concerned. Nevertheless the lesions are not ordinarily identical. The endocardial changes in lupus erythematosus are not typically granulomatous. The inflammatory component of the vascular lesions in lupus erythematosus is not so pronounced as in rheumatoid arthritis. Klemperer has stressed the importance of the "hematoxylin body" in the cardiac and other lesions of lupus erythematosus. They are not characteristic of rheumatoid arthritis.

II. SEROLOGIC TESTS FOR RHEUMATOID ARTHRITIS

A. *Historical Development.*—

In 1929 Cecil, Nicholls, and Stainsby[47,48] observed that a specific strain of hemolytic streptococcus was agglutinated in high titer by the sera of 94 per cent of patients with rheumatoid arthritis. Other workers[49,50] confirmed this phenomenon but found that it was not a type-specific reaction since many strains of hemolytic streptococci were agglutinated. The prevalence of positive agglutination reaction among rheumatoid patients was not as high as reported by Cecil and his associates. In the three laboratories referred to, the positive reactions ranged from 94 to 36 per cent[48-50] and averaged 66 per cent for 2,903 cases. In 6 per cent of patients with recent hemolytic streptococcal infections and in 3 per cent of other, nonrheumatoid cases, the test was positive.

Wallis[51] reported that the sera of rheumatoid patients had a tendency to agglutinate many bacteria and even collodion particles, but the per cent positive reactions in patients who did not have rheumatoid arthritis was high.

Technical difficulties in preparing stable and reproducible suspensions of streptococci or colloidal particles that were uniform in properties from day to day rendered these tests unsatisfactory. They have been largely abandoned.

Waaler[52] in 1940 and Rose and co-workers[53] in 1948 made the observation that rheumatoid sera had the capacity to agglutinate sheep erythrocytes sensitized by rabbit antiserum. The agglutinin titer for sensitized cells was found to be much higher than for normal sheep cells. The prevalence of positive reactions, however, was still low (33 to 37 per cent). Ball[54] increased the precision of the reaction by absorbing the patients' sera with normal sheep cells before testing. Heller and associates[55,56] enhanced the sensitivity of the test and reduced the per cent false positive reactions by diluting the patients' serum with 5 per cent normal sheep serum instead of saline solution. When the titer obtained by employing sheep serum diluent was increased fourfold or greater than the titer observed when using saline diluent, the test was considered positive. By this method the positive reactions in rheumatoid patients increased to over 70 per cent and the false positive reactions fell to 5 or 6 per cent. Recently Heller and co-workers[57] reported that normal human gamma globulin sensitized tannic acid–treated sheep erythrocytes; consequently, rabbit antiserum could be eliminated from the reaction.

A new development which may lead to a more accurate diagnostic procedure and, moreover, may afford a keener insight into the pathogenesis of rheumatoid arthritis is the observation, made independently by several workers in 1954, that the sera of patients with rheumatoid arthritis are deficient in an inhibitor of the agglutination-activating factor present in most normal human sera.[57-59]

B. *Nature of the Active Factor.*—

To date, no definite information has been obtained about the chemical nature and properties of the agglutination-activating factor. It has been reported to be found variously in the beta globulin fraction of serum proteins,[60] in the beta-gamma fraction,[53] and in fraction III of Cohn.[57] Some purification of the factor (sixteen- to fiftyfold) has been reported[60,61] although lack of a good quantitative assay method makes it difficult to determine accurately increased specific activity of preparations from serum. Still more obscure are the biologic nature and mode of action of this substance. Gorrill and Hobson[62] have concluded that the active factor has properties that resemble the C′4 component of complement. Heller[57] suggested that it is a true antibody which cross-reacts with components of sensitized sheep cells and human gamma globulin, the inciting antigen remaining unidentified. The presence of a naturally occurring inhibitor in normal sera has a parallel in several virus diseases including influenza.[63,64] Many enzyme systems are kept in check by the simultaneous presence of inhibitors. A trypsin-trypsin inhibitor complex has been implicated in hemagglutination.[65]

C. *Principle of the Hemagglutination Test.*—

The many modifications of the test, some of which will be discussed, have been prompted by two immediate objectives: (1) increased sensitivity without loss of specificity (reflected by false positive reactions), (2) demonstration of positive reactions early in the disease when diagnostic help from the laboratory would be most useful.

The principle of the test resides in the agglutination of sheep cells sensitized with amboceptor insufficient to cause agglutination until the patient's serum is added to the system. The effect of the common heterophil or Forssman antibodies is eliminated either by differential agglutination methods[53] or by absorption of these antibodies by contact with normal sheep cells.[54] All reagents except the sheep cells are heated at 56° C. for thirty minutes to inactivate heat-labile complement components.

D. *Various Modifications of Test.*—

For purposes of providing a framework for discussion of the several modifications of the test, a most recent modification, that by Ziff and associates,[53] will be outlined. (a) A 3 per cent suspension of sheep cells is titrated against the amboceptor in stepwise dilutions of 1:100, 1:200, 1:300, and so forth. The agglutination end point thus determined is called the basic agglutination titer for this lot of cells. (b) The 3 per cent suspension of cells is sensitized with an equal volume of amboceptor, this containing one-half the concentration required at the basic agglutination end point. (c) The serum to be tested is dialyzed against a citrate phosphate buffer pH 5.8 and M/150 with respect to phosphate. The precipitated euglobulin thereby obtained is centrifuged, washed with buffer, and taken up into solution in saline. The euglobulin solution is then heated to 56° C. for thirty minutes and absorbed twice at 37° C. with an equal volume of normal sheep cells. (d) Doubling dilutions beginning with 1:14 are made usually to about 1:2,000 and an equal volume of sensitized sheep cells added to each tube. The tubes are placed in the icebox overnight and read in the morning. Ziff and associates recorded gross agglutination visible to the naked eye ranging from a solid clump of fine granular clumping near the end point. A titer of 1:28 has been chosen as diagnostic.

Variations of the hemaggluntination method utilize the following reagents:

1. *Sheep cells*: Sheep cell suspensions vary from 3 per cent[53,58] to 0.5 per cent.[55,56]

2. *Amboceptor*: This term refers to antisheep erythrocyte rabbit serum. Although Rose[53] and others have based their sensitizing concentration of amboceptor on the *hemolytic* titer of rabbit antiserum, most methods base the sensitizing dose on the *agglutination* titer of the antiserum.[66] Amboceptor concentrations used by different workers vary from one-half to one-twentieth that of the basic agglutination titer end point.[56] Heller's gamma globulin sensitization method uses 2.5 mg. of fraction II (Cohn) to sensitize 1 ml. of 33 per cent sheep erythrocyte suspension. The indirect method of adjusting the sensitizing dose of amboceptor by titrating the sheep cells against a known rheumatoid serum to give a repeatable titer has also been used.[67] In our experience the latter has given the highest precision for use in isolation procedures, but is not necessary for diagnostic tests.

3. *Serum diluent*: In most procedures the diluent used is saline solution, but Heller and associates[56] have employed 5 per cent sheep serum as well as saline solution as aforementioned.

E. *Chemical Nature of the Inhibitor.*—

The inhibition of agglutination-activating factor observed by Heller[57] has become the basis of a related diagnostic test for rheumatoid arthritis. Ziff and associates observed that the euglobulin fraction from normal sera (obtained in the same manner as from rheumatoid sera) inhibited hemagglutination by known positive rheumatoid sera, whereas rheumatoid sera uniformly lacked this inhibitor. Interest in the nature of inhibitor has been stimulated by Heller's announcement[57] that normal human gamma globulin (Cohn II) contained the bulk of inhibitory activity. Williams and associates[59] have confirmed the inhibitory activity of human gamma globulin, but find that a large part of the activity can be extracted from the gamma globulin with tertiary butanol-water mixtures. The extract has an active peptide containing glycine and another amino acid as yet unidentified. Glycyl glycine in concentrations as low as 10 μ per milliliter has been observed to inhibit activity against partially purified activating factor. A wide variety of other peptides have shown no activity. Glucosamine exhibits some activity. The supernatant of human fraction II (Cohn) has been found in this laboratory to possess greater specific activity (based on nitrogen content) than gamma globulin (fraction II).

F. *Reported Results of Serologic Test.*—

The results reported by authors employing various modifications of the hemagglutination test are listed in Table I.

The reports indicate a wide range of prevalence of positive tests in patients with rheumatoid arthritis (33 to 100 per cent). Employment of the euglobulin or cold globulin fraction of rheumatoid serum yields the highest percentage of positive tests. Both methods probably depend on removal of inhibiting substances for their effectiveness. Included in our series[59] are thirteen rheumatoid patients whose sera yielded a negative hemagglutination test by the Heller method. Eight of these became positive when the euglobulin fraction was tested.

G. *Effect of Age, Sex, Activity, Duration, and Type of Arthritis on Hemagglutination Test.*—

Analysis of the various series with respect to age, sex, activity, and duration of disease yields interesting information. Ball[46] and Alexander and de Forest[67] found that the test is negative twice as frequently in females as in males. By the Rose and Heller modifications, very few positive tests were found in juvenile rheumatoid arthritis. Ziff and associates reported six of twelve such cases positive. The Rose, Ball, and Heller methods usually are not positive until eighteen months[67] after the onset of the disease, but Ziff reported positive tests in each of six cases of less than six months' duration.

The test is nearly always positive in patients with subcutaneous nodules. Spondylitis accompanied by peripheral joint manifestations almost always yields negative tests by all methods.[53,70] This has been so striking as to suggest that the Marie-Strümpell type of spondylitis may be unrelated to peripheral rheumatoid arthritis. When psoriasis is associated with rheumatoid arthritis,

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the test is usually negative.[46,55,69,74] Even more puzzling is the failure of the patient's response to influence the result of the hemagglutination reaction. Remissions, spontaneously occurring or allegedly induced by cortisone, corticotropin, gold compounds, phenylbutazone, or salicylates,[46,74,76,77] are not accompanied by conversion of a positive to a negative test.

TABLE I. HEMAGGLUTINATION TEST FOR RHEUMATOID ARTHRITIS: RESULTS OBTAINED WITH VARIOUS PROCEDURES

METHOD	AUTHORS AND DATES		REF.	RHEUMATOID ARTHRITIS		CONTROLS	
				NO. CASES	% POSITIVE	NO. CASES	% POSITIVE
Waaler	Waaler	1940	52	77	33	202	4
Rose	Rose et al.	1948	53	43	37	67	4
Rose	Brown et al.	1949	69	82	49	83	1
Rose	Jawetz and Hook	1949	70	78	23	82	2
Heller	Heller et al.	1949	55	54	67	111	2
Rose	Miller et al.	1949	71	21	68	23	35
Rose	Sulkin et al.	1949	72	35	45	113	1
Ball	Ball	1950	54	286	49	609	2
Rose	Dordick and Wasserman	1950	73	21	61	181	12
Ball	Svartz and Schlossmann	1950	74	180	90	283	4
Rose	Wager	1950	75	92	61	1,049	2
Rose	Scott	1952	76	124	60.5	172	8
Ball	Ball	1952	46	642	44	1,301	2.5
Heller	Heller et al.	1952	56	114	85	245	2
Cold globulin	Svartz and Schlossmann	1953	68	50	100	45	0
Heller (gamma globulin sensitizing)	Heller et al.	1954	57	62	71	265	5
Ball	Alexander and de Forest	1954	67	56	77	242	0.4
Euglobin agglutination	Ziff et al.	1954	58	84	92	104	2
Absence of euglobulin inhibition	Ziff et al.	1954	58	83	100	104	5
Ziff euglobulin	Williams et al.	1954	59	29	79*	22	0
Ziff euglobulin	Williams et al.	1954	59	29	93†	22	0

*Titer of 1:16 considered positive.
†Titer of 1:4 considered positive.

The relationship of sensitized sheep cell agglutination reaction to the pathogenesis and degree of activity of the disease process remains obscure. Recent advances have been directed toward increasing its sensitivity, that is, to produce a higher percentage of positive tests in rheumatoid arthritis without increasing the false positive tests. It remains highly specific except for the high incidence of positive reactions in infectious hepatitis[55,78] and sporadic positive tests in some of the so-called "collagen diseases." Encouraging also is the increasing incidence of positive tests in the first few months of the disease. This refinement will unquestionably augment the diagnostic usefulness of this test. The occurrence of positive hemagglutination reaction in juvenile rheumatoid arthritis is another attribute that will add to the importance of this serologic test.

Unfortunately, the agglutination reaction cannot be used as an index of the activity of the disease process. Although several authors have reported a higher incidence of positive reactions in active cases than in inactive ones, serial tests on the same patients have failed to reflect the activity of the disease.[77] Moreover, old "burned-out" cases may continue to show elevated titers.

H. *Comment.*—

The finding of naturally occurring inhibitors to the agglutination-activating factor in normal people and their uniform absence in cases of rheumatoid arthritis opens new possibilities of gaining insight into the pathogenesis of the disease. If, as Heller suggested, the agglutination-activating factor is a true antibody and the sensitized sheep cell merely provides a structure chemically similar to the antigen that had sensitized the patient, then it would not be surprising that high titers persist for years and are unrelated to disease activity or host response. However, if the absence of normal inhibitors has significance, it may represent the failure of an important defense mechanism, either immunologic of homeostatic. It remains to be determined whether the absence of inhibitor is genetically conditioned or the result of exhaustion of a defense mechanism under chronic stress or of its destruction by an adaptative enzyme.

Future exploration of the problem will depend on adequate purification and characterization of the interacting components of this complex system. Accurate evaluation of these steps is still dependent on a semiquantitative method of assay. The precise definition of the immunologic or enzymatic specificity of one or more of the components would immeasurably hasten the solution of the relationship of the sheep cell agglutination phenomenon to rheumatoid arthritis.

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III. TREATMENT OF RHEUMATOID ARTHRITIS

Modern treatment of rheumatoid arthritis consists of a comprehensive, individualized program and not merely of the administration of one or two antirheumatic agents. It is beyond the limits of this review, however, to describe the many components of total, adequate care and management. Emphasis will be given to a consideration of the preparations which have been used most extensively during the past five years (July, 1949-June, 1954). Special care has been taken to include conflicting opinions and controversial evidence. We make no pretence of knowing how to chart the wisest therapeutic course in the complex network of divergent pathways. It is clear, however, that the completely satisfactory antirheumatic agent has not yet been discovered. It is apparent from the bibliography (albeit incomplete) that the search is being vigorously pursued.

A. *Cortisone, Hydrocortisone, and Corticotropin.*—

The use of cortisone in rheumatoid arthritis was introduced by Hench, Kendall, Slocumb, and Polley in September, 1948. Within the ensuing year it was found that corticotropin (ACTH) and hydrocortisone were also effective. Many other hormones and closely related steroids have been tried as substitutes but have been proved ineffective.

Qualitatively, the clinical effect and the undesirable side effects obtained by cortisone, hydrocortisone, and corticotropin are very similar, although quantitatively, as will be mentioned later, the effective doses differ. Since cortisone acetate has been used more extensively than hydrocortisone or corticotropin, this steroid will be referred to most frequently in the discussion.

1. *Nature of response*: Administration of cortisone to patients with active rheumatoid arthritis is followed quite promptly and uniformly by diminution of stiffness, pain, tenderness, and later swelling. Joint effusions recede and often disappear. Mild flexion deformities are corrected. Muscular coordination and range of motion of affected joints increase. Patients who are incapacitated because of active inflammatory (reversible) joint disease often are restored to self-sufficiency and employability. Systemic symptoms such as weakness, fatigue, anorexia, fever very often subside, and abnormal laboratory findings such as elevated sedimentation rate, C-reactive protein, increased serum globulin, and anemia generally approach or return to normal. The sheep red cell and hemolytic streptococcal agglutination reactions of rheumatoid serum do not however disappear with hormone therapy and clinical improvement.[79,80]

2. *Effect on lesions*: Some of the pathologic processes of the disease may be suppressed but only few are abolished or consistently arrested. Moreover, certain severe lesions such as nonnecrotizing vasculitis or polyarteritis nodosa have been reported to appear or become activated or intensified during administration or withdrawal of cortisone.[81,18,37,22] The inflammatory reaction in the synovial membrane subsides but does not completely resolve.[82] Norcross and associates[83] reported that the nonspecific lymphocytic infiltrates in the skeletal muscles decrease. Superficial hyperplastic lymph nodes diminish in size and may become no longer palpable. An enlarged spleen may become reduced to normal size. Subcutaneous nodules often become softer and smaller and sometimes disappear. In many cases they persist, and not infrequently new nodules appear during cortisone therapy.[84] Erosion of cartilage and destruction of subchondral bone advance and may appear on x-ray film for the first time during cortisone therapy despite clinical and laboratory signs of improvement.[85-87]

3. *Withdrawal reactions*: When cortisone is abruptly discontinued or its dose substantially lowered, signs and symptoms of withdrawal will generally appear.* The withdrawal reaction may be reduced by tapering the dose so as to promote restitution of normal pituitary-adrenocortical function. Withdrawal symptoms may consist of accentuation of the arthritis, appearance of constitutional symptoms, or both. Generalized symptoms may include weakness, fatigue, anorexia, abdominal pain, diarrhea, nausea and vomiting, headache, fever, chills, emotional instability, paresthesia, and mental depression. The symptoms disappear promptly when the hormone is reinstituted.

4. *Dose*: Cortisone acetate and hydrocortisone (free alcohol) are used most commonly because they are effective when administered orally. The latter

*See section III, A, 9 (Limitations).

steroid is more potent than cortisone acetate and may therefore be administered in doses 65 to 80 per cent that of cortisone, without loss of effectiveness.[88,89] Hydrocortisone acetate is much less potent than the first two steroids mentioned and therefore is not used systemically. Its use locally, injected into joints, will be mentioned later. Corticotropin (either aqueous or in gel) must be administered parenterally.

The large priming and suppressive doses of cortisone acetate, in use several years ago, have been abandoned. It was observed that undesirable side effects and withdrawal symptoms are reduced in frequency and severity when the dose is restricted. Hench recommended beginning with a suppressive daily dose of 40 to 75 mg. for men, 20 to 35 mg. for menopausal women, 30 to 50 mg. for other women, and 15 to 30 mg. for children. The higher doses in these ranges are given to patients with severer disease. After one to two weeks, or as soon as definite antirheumatic response is obtained, the dose is lowered in decrements of 12.5 to 2.5 mg., depending on the size of the initial dose. The rate of reduction will depend on the patient's reaction and should be individualized. The daily level of maintenance should not exceed 65 mg. for men, 35 mg. for postmenopausal women, 45 mg. for other women, and 25 mg. for children. Larger doses may be used temporarily when exacerbation occurs.[91]

The comparable dose of corticotropin is about 40 per cent of the cortisone dose; for example, a patient requiring 50 mg. of cortisone acetate by mouth daily will need 20 U.S.P. units of aqueous corticotropin intramuscularly in divided doses. When corticotropin gel is used, the daily dose is somewhat lower and injections are given only once daily or every other day.

An attempt should be made to discontinue hormone therapy periodically in order to determine whether a remission has supervened.

5. *Results*: The results published in the English literature during the four years from 1950 through 1953 have been reviewed, and reports presenting data which permitted the desired analysis are listed in Table II. Series in which cortisone or corticotropin was administered concurrently with other antirheumatic agents such as gold compounds or phenylbutazone were not included. Only those authors who utilized the method of grading therapeutic responses adopted by the American Rheumatism Association reported their results uniformly in four categories. Six series, comprising 134 cases, were graded in this manner:

Remission (Grade I)	6.7 per cent
Major improvement (Grade II)	32.8 per cent
Minor improvement (Grade III)	37.3 per cent
No improvement (Grade IV)	23.1 per cent

In the corticotropin-treated group, four series consisting of sixty-four patients were graded as follows:

Remission (Grade I)	10.9 per cent
Major improvement (Grade II)	37.5 per cent
Minor improvement (Grade III)	32.8 per cent
No improvement (Grade IV)	18.8 per cent

In order to utilize all reported results listed in Table II, two general categories were made; namely, "good response," which included remissions and major improvement, and "unsatisfactory response," which included mild and no improvement. In the group treated with cortisone, twelve series consisting of 422 patients reported good response in 61 per cent and unsatisfactory response in 39 per cent. In the corticotropin-treated group, seven series consisting of 115 patients reported good response in 57 per cent and unsatisfactory response in 43 per cent.*

6. *Causes for discontinuance*: In general, hormone therapy may be abandoned for one of three reasons: (1) results are insufficient to warrant continued treatment, (2) major undesirable side effects or complications develop, and (3) remission of disease makes further hormone unnecessary. In seven reported series, totaling 216 patients, analyzed by Hench and Ward[91] cortisone was discontinued in 10 to 15 per cent of cases for reason (1) ; in 10 per cent for reason (2); and in 5 to 10 per cent for reason (3). In the opinion of other observers only 25 per cent of patients can be maintained in a state of adequate improvement on prolonged cortisone therapy. Some believe that this estimate should be raised to 50 per cent.[92]

7. *Control studies*: A controlled study of the therapeutic value of cortisone as compared to aspirin in the early stages of rheumatoid arthritis was conducted by the Medical Research Council of Great Britain and the Nuffield Foundation. For one year, thirty patients were treated with cortisone and thirty-one with aspirin. The carefully measured, objective clinical improvement and increase in functional capacity were quite similar in both groups. There was no "material difference" in the response obtained by these two agents save that a greater rise in hemoglobin and a greater fall in the sedimentation rate were observed with cortisone than with aspirin. The British cooperative study group reached the conclusion that "for practical purposes, there appears to have been surprisingly little to choose between cortisone and aspirin."[93]

This statistically disciplined study, made on patients who had rheumatoid arthritis for less than one year, has led to conclusions which are not wholly compatible with the impression of experienced clinicians in this country. Many patients who have persistently failed to improve and, moreover, whose arthritis was steadily getting worse on aspirin therapy experienced striking benefit from cortisone. When cortisone was withdrawn and replaced by large doses of aspirin (4 to 5 Gm. daily), relapse occurred. Suppression was again effected by reinstituting cortisone. It may be that aspirin has been considered inferior to

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*In comparing results reported by different authors, it is well to give special consideration to the composition of each series and to the criteria for improvement used by the authors. Factors which may favor improvement in rheumatoid arthritis are: mild degree of joint involvement, duration of arthritis of less than one year,[90] and age younger than 30 to 40 years.[84,90] Some factors contribute to an unfavorable result. It is unreasonable to expect marked improvement in joints that have undergone irreversible changes such as cartilaginous or osseous destruction, deformity, or ankylosis. The most dependable criteria for improvement are objective changes in the joints. The least dependable are subjective reports by the patient. Of intermediate value is alteration in the functional capacity of the patient. Unfortunately, many reports have failed to take these important factors into consideration.

TABLE II RESULTS REPORTED IN 720 RHEUMATOID PATIENTS TREATED WITH CORTISONE AND/OR CORTICOTROPIN (1950-1953)

AUTHORS	REF.	HORMONE USED	AVERAGE MAINTENANCE DOSE (MG./DAY)	FOLLOW-UP PERIOD	TOTAL NO. CASES	RESULTS (PERCENTAGE)				A.R.A. GRADING USED
						GOOD RESPONSE		UNSATISFACTORY RESPONSE		
						REMISSION	MAJOR IMP.	MINOR IMP.	SAME OR WORSE	
Gewalli	100	Cort.	50–75	1–3 yr.	20	50	35	15		No
Hench et al.	121, 82	ACTH	100	2 mo.	6	100		0		No
Davison	101	Cort.	50–100	1 mo.	18*	66.7			33.3	No
Steinbrocker et al.	122	ACTH + Cort.	40–50 50–100	< 1 yr.	55	5	27	51	17	Yes
Margolis and Caplan	123	ACTH	40–60	< 1 yr.	33†	61		39		Yes
Copeman et al.	102	Cort.	37½–100	< 1 yr.	20	60		40		No
Ward et al.	103	Cort.	25–100	< 1 yr.	73	65		34	1	No
Boland	104, 105	Cort.	25–100	6–15 mo.	60*	80		20		No
Fischer and Gillmor	106	ACTH	40	On R_x	24	8.3	41.7	37.5	12.5	Yes
Fischer and Gillmor	106	Cort.	100	On R_x	21	0	52.4	38.1	9.5	Yes

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Bilka	124	Cort.			50	65		35		No
Clark et al.	112	Cort.	25–200	< 2 yr.	39*	0	12.8	66.7	20.5	Yes
Clark et al.	112	ACTH	40–100	< 2 yr.	17*	0	11.7	47.1	41.2	Yes
West and Newns	19	Cort.	50–75	19 mo.	27	0	14.8	14.8	70.4	Yes
Price et al.	125	Cort.	25–75	< 2 yr.	65	74		22	4	No
Price et al.	125	ATCH		< 2 yr.	12	75		15		No
McGavack	107	Cort.		1 yr.	12	33.3	16.7	33.3	16.7	Yes
McGavack	107	ACTH		1 yr.	5	20	60	20	0	Yes
Holbrook et al.	108	ACTH + Cort.	40 100	2 wk.	60	26.7	70		3.3	No
Homburger and Bonner	113	ACTH	100		18	22.2	50	16.7	11.1	Yes
Homburger and Bonner	113	Cort.	100		11	0	63.6			Yes
Norcross et al.	109	Cort.	25–74		24	20.8	62.5	16.6	0	Yes
Levin et al.	18	ACTH + Cort.	25–65 80	18 mo.	50	8	38	38	16	Yes

*Cases of spondylitis unassociated with peripheral rheumatoid arthritis were eliminated.
†Of the 56 patients in authors' series, 23 were treated with corticotropin and gold simultaneously; hence only 33 patients are listed in this table.
Imp. = Improvement ACTH = Corticotropin A.R.A. = American Rheumatism Association
Cort. = Cortisone R_x = Treatment

cortisone simply because aspirin has been given inadequately or irregularly. But that seems an unlikely explanation in many instances. A similar control study has not been conducted in this country, and hence the authority to disagree is lacking. Nevertheless, it is difficult for many workers in this field to accept the conclusion that aspirin is as effective an antirheumatic agent as cortisone.

8. *Intra-articular injection of hydrocortisone acetate*: The prompt, local, anti-inflammatory effect of hydrocortisone acetate injected into a rheumatoid joint can be readily demonstrated in most instances. The reported number of patients injected with this steroid exceeds 1,000.[91-99] About 80 per cent of the injections are followed by moderate to marked objective clinical improvement, and in 95 per cent there are significant changes toward normal in the properties of the aspirated synovial fluid; for example, relative viscosity, volume of effusion, total leukocyte count, and tripeptidase activity. Clinical improvement begins generally on the day following injection, but, often, within three hours. The improvement lasts an average of eight days, and ranges from four to fifteen days. Repeated injections are therefore necessary. This type of treatment must be considered palliative and temporary. It is useful in cases where only a few easily accessible joints are involved or remain conspicuously less responsive than other joints to systemic measures. The usual dose for a large joint is 25 mg.; for a metacarpophalangeal joint 10 mg.; and for an interphalangeal joint 5 mg.[95] The procedure is simple and usually without hazard. Hydrocortisone acetate is distinctly superior to cortisone and is the drug of choice for this route.

9. *Limitations*: Unless a complete remission has supervened (and this occurs in less than 20 per cent of the cases), flare of the arthritis is to be expected when cortisone is withdrawn. In the unremitting type of rheumatoid arthritis the steroid may have to be given indefinitely. The hormone suppresses but does not eradicate or fully arrest the inflammatory process. As has been noted, the destructive pathologic processes often continue during the administration of cortisone.

Numerous undesirable side effects and complications resulting from cortisone have been observed (Table III). The reported incidence of side effects from prolonged therapy varies from 20 to 100 per cent depending largely on dosage used. When the daily dose is 75 mg. or more the incidence is three times as great as it is in patients taking less than 75 mg.[91] In general, women develop side effects more often than men and children more often than adults. In one series of fifty-nine patients, 70 per cent of the males and 84 per cent of the females manifested one or more of the symptoms listed in Table III.[84] Among 477 reactions reported in a collected series of 406 rheumatoid patients taking cortisone,[100-110,112] and among 497 reactions reported in 342 patients receiving corticotropin,[106-108,112-114] the *relative* incidences of the five commonest symptoms were as follows:

	CORTISONE (%)	CORTICOTROPIN (%)
1. Mental and emotional changes	22	22
2. Retention of fluid	15	21
3. Rounding of face	16	15
4. Hypertrichosis and other cutaneous manifestations	10	17
5. Diminished glucose tolerance	4	4
Total	67	79

These five categories of reactions constituted 67 per cent of all undesirable symptoms observed with cortisone and 79 per cent with corticotropin.

TABLE III. SIDE EFFECTS AND COMPLICATIONS OF PROLONGED CORTISONE THERAPY

Mental symptoms	Delayed wound healing
Facial rounding (moonface)	Headache
Abnormal fat deposits	Weakness
Fluid retention (edema)	Menstrual disorders
Excessive appetite and weight gain	Accentuated menopausal symptoms
Hypertrichosis	Neuropathy (including neuritis, paresthesias)
Acne	Fractures (osteoporosis)
Striae	Peptic ulcer (activation, perforation, hemorrhage)
Ecchymosis	
Increased sweating	Decreased glucose tolerance
Pigmentation	Hypopotassemia
Dry, scaly skin	Adrenal insufficiency
Thinning scalp hair	Polyarteritis nodosa
Increased blood pressure	Impaired renal function
Tachycardia	Lupus erythematosus–like changes
Thrombophlebitis	Hepatomegaly (children)
Decreased resistance to infection	Abdominal distention (children)

Most of the changes are minor and many subside when the dose is reduced. Almost all side effects are reversible and disappear when the hormone is discontinued.

Cortisone administration depresses the output of corticotropin by the anterior pituitary body; consequently, endogenous adrenocortical secretion is suppressed. This is evidenced by a fall in the urinary 17-ketosteroid excretion during therapy and by manifestations of adrenal insufficiency when cortisone is abruptly withdrawn. The adrenal cortex atrophies and its lipid content falls appreciably when cortisone is given.[30] Nevertheless, it is noteworthy that the majority of patients given continuous cortisone therapy for several years show no signs of adrenal cortical insufficiency.[84] While cortisone is being withdrawn it is important to administer corticotropin either intramuscularly or intravenously in quantities sufficient to restore adequate endogenous adrenocortical secretion.

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As stated previously, in a collected series of 422 rheumatoid patients treated with cortisone, 39 per cent experienced slight or no improvement. Some patients may show a satisfactory response during the first few months of therapy and then become refractory.

Certain pathologic conditions unrelated to rheumatoid arthritis may be activated or intensified when cortisone is administered. Active pulmonary tuberculosis, other bacterial or viral infections, diabetes mellitus, peptic ulcer, and other disorders listed later as contraindications are examples.

Hench and Ward[91] found references to thirty-two rheumatoid patients who died from various causes during or sometime after conclusion of treatment. Nine of these deaths were definitely or probably related to treatment. The causal relationship of the other deaths was possible but doubtful, coincidental, or not clear. Of the nine related deaths, four resulted from acute postoperative adrenal insufficiency,[115-117] one patient committed suicide,[118] one died from masked overwhelming pneumococcus infection,[84] one died during an epileptic seizure nineteen days after cortisone was discontinued[30]; one child died during a tonic convulsion,[119] and one patient following gastric hemorrhage.[120]

10. *Indications*: Most suitable for cortisone therapy are patients who have not responded adequately to simple measures, who have active progressive arthritis but joint changes that are reversible, who do not require large maintenance doses (above 60 mg. per day) for satisfactory control, and who present no contraindications.

11. *Contraindications*: Certain contraindications to prolonged cortisone administration are absolute and others are relative. In the former category are active tuberculosis, psychosis or severe psychoneurosis, active peptic ulcer, severe microbial infections that cannot be controlled by antibiotics, and Cushing's syndrome. The relative contraindications consist of arrested tuberculosis, cardiovascular disease, renal insufficiency, moderate or severe diabetes mellitus, thromboembolic phenomena, osteoporosis, and convulsive disorder.[91,92]

12. *Suggested cortisone precautions*: Based on a review of the literature and our experience the following admonitions seem indicated:

(1) Do not try cortisone before giving the patient a trial on simple measures such as aspirin, rest, splints, corrective exercise, physical therapy, and assurance.

(2) Do not administer cortisone to a rheumatoid patient who has mostly inactive disease, irreversible joint changes, and deformities.

(3) Do not administer cortisone in the presence of known contraindications.

(4) Do not fail to check for each of the contraindications.

(5) Do not treat a rheumatoid patient with cortisone alone; hormone therapy should be part of an individualized comprehensive regimen.

(6) Do not try for maximal antirheumatic results; be content with satisfactory results. The likelihood of inducing side effects or complications varies with the amount of hormone given.

(7) Do not initiate therapy with very large priming doses, for example, over 100 mg. daily.

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(8) Do not continue large initial suppressive doses (75 mg. or more) for more than a few weeks.

(9) Do not be lured by the disease or the patient to a daily maintenance dose above 75 mg.

(10) Do not increase the dose of cortisone when the patient has symptoms of hypercortisonism simulating a flare of arthritis.

(11) Do not discontinue therapy because of minor undesirable side effects such as hypertrichosis, rounding of face, acne, or amenorrhea.

(12) Do not ignore certain warnings of serious side effects or complications such as mental changes, hypertension, symptoms of peptic ulcer, bone fracture, premonitory signs of lupus erythematosus, or polyarteritis nodosa.

(13) Do not neglect to administer adequate doses of cortisone to a patient who is subjected to major surgical operation, severe infection (for which satisfactory antibiotic therapy is available), or other types of stress and who received cortisone for more than four weeks during the preceding six months.

(14) Do not continue cortisone when the patient develops a serious virus infection for which there is no satisfactory antibiotic agent. Cortisone dosage should be tapered and withdrawn in two or three days and corticotropin simultaneously administered by intravenous route.

(15) Do not discontinue cortisone abruptly.

B. *Phenylbutazone.*—

Phenylbutazone (Butazolidin) is a pyrazole derivative synthesized by H. Stenzl of the Geigy Company, Switzerland. It was found to possess analgesic, antipyretic, and anti-inflammatory effects in rheumatoid arthritis, spondylitis, and other rheumatic diseases. Phenylbutazone was first used in 1949 in combination with aminopyrine (Irgapyrine or Butapyrin) and in 1951 it was produced alone. Since 1952 phenylbutazone has been used in this country largely to the exclusion of Butapyrin. To date, published reports include more than 2,500 patients treated with phenylbutazone.[21,126-171] Chemically it is designated as sodium 4-butyl-1, 2-diphenyl-3, 5-pyrazolidinedione.

1. *Nature of response*: The earliest sign of improvement is reduction in stiffness which occurs within the first twenty-four hours. Pain on motion and joint tenderness recede more gradually during the following few days. Synovial effusion was reported to disappear in two to three weeks of medication.[171] Systemically patients report increased appetite, vigor, and sense of well-being. Subcutaneous nodules remain unaltered.[172] The erythrocyte sedimentation rate does not fall consistently and rarely returns to normal levels. No evidence is advanced that phenylbutazone halts or retards the progression of pathologic processes in rheumatoid arthritis. The intimate mechanism of action of phenylbutazone is unknown. One week after the drug is withdrawn the symptoms of arthritis return.

2. *Pharmacology and dosage*: Phenylbutazone is completely absorbed from the gastrointestinal tract and the maximum plasma concentration is attained within two hours after oral administration. When the drug is given intramuscularly, absorption is slower and peak plasma levels are not reached

TABLE IV. REPORTED RESULTS IN 1,008 RHEUMATOID PATIENTS TREATED WITH PHENYLBUTAZONE

AUTHORS	REF.	DOSE RANGE (MG./DAY)	ROUTE OF ADMINISTRATION	FOLLOW-UP PERIOD (MONTHS)	NO. OF CASES	RESULTS (PERCENTAGE)				A.R.A. GRADING USED
						GOOD RESPONSE		UNSATISFACTORY RESPONSE		
						REMISSION	MAJOR IMP.	MINOR IMP.	SAME OR WORSE	
Cudkowicz and Jacobs	130	Less than 1,000	I-M	Less than 4	34	59			41	No
Strazza and Ressetar	164	200–800	I-M I-V Oral	6–12	43	14	55.8	27.9	2.3	Yes
MacKnight et al.	147	200–800	Oral	—	49	0	42.8	40.7	16.3	Yes
Kuzell et al.	142	400–1,600	I-M Oral	0–30	163	6	52.8	24.5	16.6	Yes
Freeland et al.	136	400–600	Oral	1	164	44		26	29	No
Stephens et al.	163	400–1,600	Oral	9	115	41		9	50	No
Davies et al.	133	1,000	I-M	Less than 6	16	87.5			12.5	No
Currie et al.	132	200–400	Oral	—	424	30			70	No

I-M = Intramuscular
I-V = Intravenous
A.R.A. = American Rheumatism Association

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until six to ten hours after injection.[171] Nevertheless, some observers report that more rapid clinical improvement follows intramuscular rather than oral administration.[140] The drug is almost completely metabolized in the body and consequently appears in urine only in minute amounts. As daily oral administration continues, the plasma concentration rises progressively, and a plateau is reached on the third or fourth day and sustained thereafter. With the identical dose, the plateau plasma level will vary widely from one person to another. Thus, Brodie and his associates[171] found that on a daily dosage of 800 mg. of phenylbutazone, the plasma concentration from the fourth to fourteenth days of medication ranged from 60 to 150 mg. per liter among a group of subjects; yet it remained fairly constant in any one person of the group. The plasma concentration fails to increase in proportion to daily oral dose after the dose exceeds 800 mg. At a dosage of 1,600 mg. daily the plasma level is only 10 per cent higher than at 800 mg. At 800 mg., the level is only slightly higher than at 400 mg. There seems little to be gained, therefore, by exceeding an oral dose of about 600 mg. daily. Many authors recommend doses between 200 and 400 mg. per day. The dose for intramuscular route is 1.0 Gm. daily.

Phenylbutazone causes retention of sodium, chloride, and water but does not affect potassium excretion. The fall in red blood cell count, hematocrit, and hemoglobin associated with phenylbutazone administration is believed to be due to hemodilution and not to increased destruction or reduced production of erythrocytes.[171]

3. *Results*: Approximately 40 per cent of the reported cases treated with phenylbutazone alone and recorded in a manner permitting comparative analysis consisted of patients with rheumatoid arthritis. Table IV presents 1,008 such cases collected from eight reports. In three of the reports, consisting of 255 cases, the grading adopted by the American Rheumatism Association was used. The results are as follows:

Remission (Grade I)	6.3 per cent
Major improvement (Grade II)	51.3 per cent
Minor improvement (Grade III)	28.2 per cent
No improvement (Grade IV)	14.1 per cent

In the remaining five reports that did not use this classification 534 patients are included. Fifty per cent of the cases showed a good response and 50 per cent an unsatisfactory response. Cases included in a control study (133,136) were too few to permit adequate comparison.*

4. *Toxicity*: Thirty-two per cent of all patients taking phenylbutazone develop some toxic reactions, and in 38 per cent of these, the symptoms are severe enough to cause interruption or termination of therapy. These data are based on a review of 2,301 cases collected from sixteen papers.[127,130,132,133,136-139,142,143,146,147,149,152,162,163]

*The factors, enumerated in the footnote in section III, A, 5 (Results), that may significantly affect results again failed to receive the necessary consideration in the papers on phenylbutazone.

TABLE V. REPORTED DEATHS FROM PHENYLBUTAZONE (DECEMBER, 1952, TO APRIL, 1954)

AUTHORS	REF.	AGE	SEX	DIAGNOSIS	DURATION OF DISEASE	DOSE (MG./DAY)	DURATION OF TREATMENT	CAUSE OF DEATH
Dilling	134	53	F	R.A.	17 yr.	400–600	8 days	Agranulocytosis
(Brit. M. J.)	167	75	F	R.A.	20 yr.	"2 tablets TID"	8 days	Peptic ulcer with hemorrhage
Leonard	145	64	F	R.A.	Less than 1 yr.	600	14 days	Aplastic anemia
Benstead	128	71	F	R.A.	Not stated	200–400	14 days	"Gas gangrene"
Benstead	128	65	F	R.A.	17 yr.	600	15 days	Peptic ulcer with perforation
Nathan et al.	170	60	F	R.A.	"Many years"	800	17 days	Hypersensitivity with rash
Steinberg et al.	160	52	F	R.A.	15 yr.	400	1 mo.	Agranulocytosis
O'Brien and Storey	21	73	M	R.A.	5 yr.	400	5 wk.	Hypersensitivity with angiitis
(Brit. M. J.)	167	57	F	R.A.	1½ yr.	600	6 wk.	Agranulocytosis
Etess and Jacobson	135	74	M	R.A.	33 yr.	600	2 mo.	Agranulocytosis
(Lancet)	169	44	F	Not stated				Agranulocytosis

R.A. = Rheumatoid arthritis

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Of the diverse toxic reactions reported, 77 per cent consisted of the six principal symptoms listed below and the remainder included miscellaneous reactions such as stomatitis, vertigo, lethargy, and rarely fever, hepatitis, or hypertension.

Six Principal Toxic Reactions to Phenylbutazone

1.	Gastritis, nausea, vomiting, or diarrhea	30 per cent
2.	Fluid retention (weight gain or edema)	19 per cent
3.	Rash (erythematous, macular)	14 per cent
4.	Anemia, leukopenia or agranulocytosis	7 per cent
5.	Purpura or thrombocytopenia	4 per cent
6.	Peptic ulcer or gastrointestinal bleeding	3 per cent
	Total	77 per cent

5. *Deaths*: Eleven deaths attributed to phenylbutazone are reported in the English literature from December, 1952, to April, 1954 (Table V). Five were due to agranulocytosis, one to aplastic anemia, two to peptic ulcer with hemorrhage or perforation, two to hypersensitivity, and one to "gas gangrene."

It is striking that all deaths but one occurred among patients with rheumatoid arthritis. (The diagnosis in the eleventh case is not stated.) Although the exact prevalence of rheumatoid arthritis among all diseases treated with phenylbutazone is not known, the predominance of rheumatoid arthritis in the fatal cases warrants careful consideration. Patients with rheumatoid arthritis are often subjected to prolonged medication (salicylates, gold compounds, adrenocortical hormones), either prior to or concurrently with phenylbutazone, that may predispose them to serious complications. Possibly, the hematopoietic and gastrointestinal organs of rheumatoid patients are especially vulnerable.

Nine of the patients who died were women. The sex ratio of all rheumatoid patients treated with phenylbutazone is not known, however. No deaths occurred within the first seven days of treatment. Six of the eleven deaths occurred during the second and third weeks of therapy, four deaths between the fifth and eighth week. The time of death in the eleventh case was not stated. The daily doses of phenylbutazone in the fatal cases were not excessive.

6. *Similarities and differences between cortisone and phenylbutazone*: Although there are a few similarities between these two antirheumatic agents, they appear to be superficial. The differences are more fundamental.[173] Both agents are effective in rheumatoid arthritis, ankylosing spondylitis, and gout. Both induce retention of sodium and water so that patients with organic heart disease and diminished functional cardiac capacity may develop congestive heart failure while taking these compounds. Both may reactivate peptic ulcers, with resulting hemorrhage or perforation in some cases. The mechanism of action is obscure, as yet, in both. On the other hand, phenylbutazone is not a hormone. It is not a steroid but a synthetic pyrazole derivative. Phenylbutazone does not maintain adrenal function in hypophysectomized animals.

It does not alter 17-ketosteroid urinary excretion. It does not cause eosinopenia or lymphopenia. Phenylbutazone does not affect the sodium or potassium content of saliva. It does not cause an increase in urinary potassium excretion. It does not change the glomerular filtration rate. Phenylbutazone is not associated with increased uropepsin excretion. Improvement in rheumatic diseases following phenylbutazone is not commonly accompanied by reduction in erythrocyte sedimentation rate or disappearance of C-reactive protein. Phenylbutazone does not increase the insulin requirements of diabetic persons. Phenylbutazone is not indicated in such nonrheumatic diseases as status asthmaticus, atopic dermatitis, drug hypersensitivity, lupus erythematosus, leukemia, and nephrosis. Cortisone does not cause anemia, granulocytopenia, agranulocytosis, thrombocytopenic purpura, stomatitis, hepatitis, anorexia, or nausea. Phenylbutazone administration is not associated with manifestations of hyperadrenocortical function such as obesity, "moonface," hirsutism, striae, acneform eruption, pathologic fractures, or increased susceptibility to microbial infection.

C. *Gold Therapy.*—

There has been a resurgence of interest in gold therapy in the past three years as it has become evident that only about 50 per cent of rheumatoid patients responded satisfactorily to adrenocortical therapy.

Since 1950, several papers on the historical aspects of gold therapy have appeared.[174-177] Gold was first used in France, Germany, and Denmark to treat pulmonary tuberculosis. The idea developed that gold might be of use in rheumatoid arthritis. This disease appeared to be a chronic infection resembling, at least, if not actually being, an atypical form of tuberculosis. Feldt in Germany and Forestier in France began giving gold preparations to rheumatoid patients in the late 1920's with fair results. In 1950 Freyberg[178] reported a series of 4,086 gold-treated rheumatoid patients collected from reports in the world literature prior to 1948. In an average of 61 per cent of these patients, the arthritis was reported to be "arrested" or "improved" after gold therapy.

Between 1950 and 1954 many additional groups of gold-treated patients have been reported. Fifteen of these reports contain sufficient details to make some degree of comparison possible, and seven include controls (Table VI).

1. *Nature of response*: Improvement with gold is gradual and not so dramatic as a satisfactory cortisone response. After several months of chrysotherapy, the patient who is responsive and can tolerate the metal compound will report less joint pain, stiffness, and tenderness. Swelling subsides, effusion may recede, and functional capacity increases. Subcutaneous nodules are unaffected and destruction of cartilage and bone is not arrested.[183]

2. *Preparations used and dosage*: A variety of gold preparations have been produced. The more commonly used compounds are sodium aurothiomalate (Myochrysine), sodium aurothioglucose (Solganol-B-Oleosum), sodium aurothiosulfate (Sanocrysin), and aurothioglycolanilide (Lauron). The last-mentioned agent is an insoluble compound, the others are water soluble.

The conventional dosage schedule consists of weekly intramuscular injections. First 10 and 25 and then 50 mg. of the compound are given weekly

until an aggregate of 1.0 to 1.5 Gm. is administered. Opinion is divided as to the "course" method of treatment and the "maintenance doses" method. Most authors, hoping to avoid relapses, favor giving maintenance doses of 50 mg. every three or four weeks following the initial series of weekly injections, provided there has been sufficient improvement. If no improvement occurs after 1.5 Gm. is given, most authorities agree that gold treatment should be abandoned.

The desirability of beginning gold therapy as early as possible in the course of the disease was stressed by Adams and Cecil,[179] who reported a 78.7 per cent remission rate in their patients treated in the first six months after onset of rheumatoid arthritis. The group treated between seven and twelve months after onset showed a 48.9 per cent remission rate. This was still better than the over-all remission rate of 44.8 per cent in all their gold-treated patients. It should be recalled that in the group of patients reported by Short and Bauer[90] who were not treated with gold, improvement resulting from general measures in those who had arthritis for six months or less occurred in 81 per cent and in those with arthritis of seven to twelve months' duration in 61 per cent.

3. *Pharmacology*: The pharmacology of gold was thoroughly discussed by Freyberg and his associates[180,181] in 1941. Gold salts are stored for protracted periods of time following repeated weekly injections and may be found in the plasma and urine ten to fifteen months after the end of a course of 50-mg. weekly injections. Circulating gold is bound to plasma protein. This gold-protein complex does not readily pass through intact vascular membranes but does penetrate inflamed tissue, such as the synovial lining of rheumatoid joints.[182] Gold is excreted chiefly in the urine and feces.

4. *Indications*: Unlike the adrenocortical hormones and phenylbutazone, gold compounds are not indicated in any of the rheumatic diseases other than rheumatoid arthritis or palindromic arthritis. Like cortisone and phenylbutazone, gold is indicated in cases where the disease is active, the abnormal changes at least partly reversible, and the patient unresponsive to conservative measures.

5. *Contraindications*: Certain contraindications to gold therapy are stressed such as severe diabetes mellitus, pregnancy, severe liver disease, nephritis, ulcerative colitis, blood dyscrasias, exfoliative dermatitis, and disseminated lupus erythematosus.

6. *Results*: Table VI presents the data from fourteen series of gold-treated patients reported between 1950-1954 in addition to Freyberg's large collection of cases mentioned previously. Several smaller series reported in recent years with data insufficient for purposes of comparison were not included.

Some method of comparing the end results is necessary. Unfortunately, many authors have not used the American Rheumatism Association classification of response to therapy. The most practical method of comparing these cases was to borrow the term "good end result" from Ragan[184] and include, under this heading, cases with remission or major improvement. Minor or slight improvement was not considered a good end result. This scoring method can be related to the A.R.A. classification. Grade I and II responses may be considered "good end result" and III and IV as "poor end results."

TABLE VI. RESPONSE OF RHEUMATOID ARTHRITIS TO GOLD THERAPY AS COMPARED WITH CONTROLS* (1950-1953)

	SERIES	REF.	GOLD OR CONTROL	GOLD PREP. USED	AVERAGE WEEKLY DOSE (MG.)	AVERAGE TOTAL DOSE (GM.)	FOLLOW-UP PERIOD (YEARS)	NUMBER OF CASES	RESPONSE (PERCENTAGE)				A.R.A. GRADING USED	NOTES
									GOOD RESPONSE		UNSATISFACTORY RESPONSE			
									REMISSION	MAJOR IMP.	MINOR IMP.	SAME OR WORSE		
Series With Controls	Adams and Cecil	179	G	SBO M	50–100	1–1.5	1.5+	106	44.8	13.2	5.7	36.3	Yes	†
			C				1.5+	83	27.7	9.6	8.8	53.9		
	Peebles Brown and Currie	195	G	M	—	0.8–1	1	38	53			47	No	‡
			C				1	67	55			45		
	Lawrence	182	G	SBO M	100–300	—	0–2	110	36.3	60		3.6	No	§ ‖
			C				0.75	30	3	73.3		23.3		
	Merliss et al.	192	G	L	—	3.3	1	27	37			63	No	¶
			C				1	44	43			57		
	Ragan	184	G	—	—	—	5	201	23	20	57		No	#
			C				5	173	31	23	46			
	Snorrason	194	G	S	250–1,000	—	5	222	75.3			24.7	No	**
			C				5	89	32.6			67.4		
	Thompson and Rowe	185	G	SBO M, S	50	1	—	42	40.5	14.6	45.2		Yes	**
			C					273	4.4	38.1	57.5			

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Series Without Controls	Batterman	188	G	L	50–150	—	0.1–3	69	11.6	26	62.4	Yes	** ††
	Egelius	196, 197	G	—	—	—	5–15	208	15.3	30.8	53.8	No	
	Gilbert and Moore	190	G	M	50	1	—	21	24	66	10	No	**
	Hersperger	174	G	M	50–100	—	—	26	23.1	69.2	7.7	No	**
	Neudorff	176	G	SBO	50	—	0–2	18	55.5	22.2	5.5	16.6	Yes **
	Nugent et al.	193	G	M	50	1	—	29	58.9	30.8	10.4	No	**
	Schwartz et al.	198	G	L	100	3	3	56	3.6	37.5	32.1	26.7	Yes **
	Freyberg	178	G	Misc.				4,086	61	24	15	—	‡‡

*Controls treated with or without salicylates and/or physiotherapy. None received adrenocortical hormones or phenylbutazone.
L = Lauron SBO = Solganol-B-Oleosum G = Gold-treated
M = Myochrysine S = Sanocrysin C = Control

†Cases with symptoms of less than one-year duration at the start of treatment. Figures refer to the status of patients at the end of the follow-up period. Earlier results were considerably better.

‡The controls include the authors' series treated with saline solution, physiotherapy, and aspirin.

§Over one-half the patients given Myochrysine developed stomatitis (63 per cent). Data do not permit computing the over-all incidence of toxicity.

||Lawrence mentioned one patient treated with large doses of gold who died with agranulocytosis prior to 1935. This patient is not included in this series of 110.

¶One patient dropped from total series of twenty-eight because full dose of gold not given.

#The classification of Ragan deals with the end results of therapy. The figures were obtained from published graphs.[184]

**Author gave prolonged maintenance therapy in contrast to courses.

††Seventeen patients were on prolonged maintenance therapy. Eighty-eight per cent had satisfactory end results.

‡‡Collection of cases from world literature prior to 1948.

Although a total of 1,173 cases (exclusive of Freyberg's 4,086 cases) were reported in the period covered in this review, the published data permitted only seven series, totaling 513 cases, to be classified by "good" and "poor end results" standards. In this group, 46.6 per cent had good end results.

Seven paired series of gold-treated and control patients are included in Table VI. The seven groups total 1,505 cases; 746 received gold and 759 were controls. Unfortunately the results were not reported in a uniform manner. Even the gross division of good and poor end results could be made in only three series.[179,184,185] The good end results in the gold-treated and in the controls, respectively, were 58 per cent (gold) and 37 per cent (controls); 43 per cent (gold) and 54 per cent (controls); 55 per cent (gold) and 43 per cent (control). In the last two pairs cited, the results are quite divergent.

The results *ultimately* obtained after prolonged chrysotherapy in some series were not superior to those observed in the control patients.[184] It should be emphasized, however, that during the period of observation, which in some instances lasted for many years, the gold-treated patients may have improved to a much greater degree than the controls. During this interval, the benefits of chrysotherapy may well have outweighed the risks.

In regard to remission rates, ten of the series reviewed here included sufficient data. This represents 865 cases, of which 226 or 26 per cent developed remissions after gold therapy.

Here again, only four paired series of gold-treated and control patients can be analyzed for remission rate.[179,182,184,185] Patients receiving gold totaled 459, and 559 were used as controls. The remission rate in the four treated groups combined was 32 per cent and in the controls 17 per cent. The range of remission rates in the gold-treated group was 23 to 45 per cent and in the control 3 to 31 per cent.

It is interesting and important to note that the reported remission rate in gold-treated patients decreased with the length of follow-up period. The series followed for two years or less (359 cases) had an average remission rate of 30 per cent, those cases (201) followed from two to five years 23 per cent, and the one series followed for five to fifteen years (208 cases) 15 per cent.

7. *Toxicity*: Many papers record toxic reactions to gold during the period covered by this review.[174-179,182,186-194]

As experience and effective measures to combat toxicity have increased, the reported fatalities from chrysotherapy have decreased strikingly. Nevertheless, the average incidence of all toxic reactions (mild and severe) in the collected series reported from 1950 to 1953 is approximately the same as the incidence reported prior to 1948.

In 1935 the mortality in some series reached 3 per cent, from 1939 to 1945 it fell to 0.4 per cent (92), and in the fourteen series reported between 1950 and 1953 (included in Table VI) there were no deaths since 1936. The average incidence of toxic reactions in 1,159 cases included in this review was 39 per cent (ranging from 5 to 64 per cent) and in 4,086 cases in Freyberg's review prior to

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1948 it was 37 per cent.* Gold therapy was discontinued because of toxicity in an average of 9 per cent (ranging from 3 to 24 per cent) of the recent series.

The six principal symptoms and laboratory signs of toxicity follow:

1. Dermatitis	49 per cent
2. Pruritus	18 per cent
3. Albuminuria	11 per cent
4. Stomatitis	4 per cent
5. Diarrhea	4 per cent
6. Leukopenia	4 per cent
Total	90 per cent

Thrombocytopenia or purpura was reported in 2 per cent of the cases reviewed. Effective agents now available to combat the more serious toxic reactions are 2, 3-dimercaptopropanol (British anti-lewisite, BAL), useful in dermatitis, thrombopenic purpura, and agranulocytosis. The toxic reactions that satisfactorily yield to cortisone therapy have not yet been clearly defined.

8. *Relapses*: Adams and Cecil[179] reported a relapse rate of 28 per cent in gold-treated patients followed for an average of forty-seven months compared with 33 per cent in the control cases followed an average of fifty-four months. This is much lower than the general relapse rate of 50 to 80 per cent reported in the tenth Review of Rheumatism and Arthritis in 1953.[92] Relapses following discontinuance of gold, unlike cortisone or phenylbutazone, occur gradually, and appear weeks to months following the end of treatment. There are no withdrawal symptoms.

9. *Comment*: There is no unanimity of opinion among equally competent and informed observers as to the drug of choice for those patients whose arthritis has failed to be satisfactorily controlled by the "conservative" general measures (rest, corrective exercise, physiotherapy, splints, and salicylates). Some physicians will choose gold, some cortisone, and others phenylbutazone. Often the decision is made for the physician by the patient's reaction to one or another of the antirheumatic agents. It is clear from the foregoing discussion that each drug may produce undesirable side effects or toxic reactions. Relapses occur sooner or later in the majority of patients after any of these medications are discontinued. There is no evidence that any of these agents has the capacity to arrest or substantially retard the pathologic processes of this disease. Obviously, none of the compounds strike at the cause of the disease, since the etiology of rheumatoid arthritis still eludes us. No one of them should be used as the sole therapeutic agent but should be one component of an individualized comprehensive plan of management.

*Incidence of toxicity is calculated here as the number of *toxic reactions* appearing among the total number of patients in the series. Although it would be preferable to determine incidence on the basis of the number of *patients* having toxic reactions, most published reports do not give this information. In six reports that include such data (174, 176, 188, 190, 192, 193), seventy-nine of 235 patients (34 per cent) had 115 symptoms of toxicity.

It should be emphasized, however, that although the cure for rheumatoid arthritis is not yet in sight, these agents together with other therapeutic measures often achieve a considerable degree of objective and subjective improvement. They frequently enhance the functional capacity of the patient, restoring him to a state of self-sufficiency and employability. The risk involved in prescribing an effective antirheumatic agent that is potentially toxic must constantly be balanced by the real risk of permitting the disease to progress relentlessly to destruction, deformity, disability, and demoralization.

D. *Preparations of Dubious or No Value.*—

Many substitutes for cortisone have been recommended since 1950 but none of the following have been found to be effective by competent and impartial observers: desoxycorticosterone acetate combined with ascorbic acid,[199-216] pregnenolone,[217-220,107,204] 21-acetoxypregnenolone,[217,230] pregnenetriolone acetate,[231] tetesterone,[236] compound S of Reichstein,[231] post-partum plasma,[237-242] placental serum,[243-246] pitressin,[247] and many others.[91]

In addition to steroid or hormonal preparations, numerous other measures have been suggested in the treatment of rheumatoid arthritis.[248]

The many articles on orthopedic management and physical therapeutic measures of proved value in rheumatoid arthritis are beyond the scope of this review.

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REFERENCES

1. Polley, H. F., and Bickel, W. H.: Punch Biopsy of Synovial Membrane, Ann. Rheumat. Dis. **10**:277, 1951.
2. Sokoloff, L., and Gleason, I. O.: The Sternoclavicular Articulation in Rheumatic Diseases, Am. J. Clin. Path. **24**:406, 1954.
3. Collins, D. H.: The Pathology of Articular and Spinal Diseases, London, 1949, Edward Arnold & Co.
4. Cruickshank, B.: Histopathology of Diarthrodial Joints in Ankylosing Spondylitis, Ann. Rheumat. Dis. **10**:393, 1951.
5. Romanus, P., and Yden, S.: Destructive and Ossifying Spondylitic Changes in Rheumatoid Ankylosing Spondylitis (Pelvo-spondylitis Ossificans), Acta orthop. scandinav. **22**:88, 1952.
6. Baggenstoss, A. H., Bickel, W. H., and Ward, L. E.: Rheumatoid Granulomatous Nodules as Destructive Lesions of Vertebrae, J. Bone & Joint Surg. **34A**:601, 1952.
7. Sherman, M. S.: Psoriatic Arthritis. Observations on the Clinical, Roentgenographic and Pathologic Changes, J. Bone & Joint Surg. **34A**:831, 1952.
8. Sokoloff, L., McCluskey, R. T., and Bunim, J. J.: Vascularity of the Early Subcutaneous Nodule of Rheumatoid Arthritis, Arch. Path. **55**:475, 1953.
9. Klinge, F.: Knotenbildung ohne "Gelenk" rheumatismus, in Lubarsch, O., and Henke, F.: Handb. d. spez. path., Anat. u. Histol., vol. 9, Berlin, 1934, Julius Springer, p. 159.
10. Kellgren, J. H., and Ball, J.: Tendon Lesions in Rheumatoid Arthritis, Ann. Rheumat. Dis. **9**:48, 1950.
11. Kestler, O. C.: Histopathology of the Intrinsic Muscles of the Hand in Rheumatoid Arthritis: A Clinico-pathological Study, Ann. Rheumat. Dis. **8**:42, 1949.
12. Sokoloff, L.: The Heart in Rheumatoid Arthritis, Am. Heart J. **45**:635, 1953.
13. Mainland, D.: The Risk of Fallacious Conclusions From Autopsy Data on the Incidence of Diseases With Application to Heart Disease, Am. Heart J. **45**:644, 1953.
14. Bauer, W., Clark, W. C., and Kulka, J. P.: Aortitis and Aortic Endocarditis, an Unrecognized Manifestation of Rheumatoid Arthritis, Proc. Ann. Mtg. Amer. Rheum. Assn., June 8, 1951, Abstr. Ann. Rheumat. Dis. **10**:470, 1951.
15. Sokoloff, L., Wilens, S. L., and Bunim, J. J.: Arteritis of Striated Muscle in Rheumatoid Arthritis, Am. J. Path. **27**:157, 1951.
16. Radnai, B.: Vascular Changes in Peripheral Nerves and Skeletal Muscles in Rheumatoid Arthritis, Acta morphol. **3**:87, 1953.
17. Cruickshank, B.: The Arteritis of Rheumatoid Arthritis, Ann. Rheumat. Dis. **13**:136, 1954.

18. Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L., and Barrett, T. F.: The Prolonged Treatment of Rheumatoid Arthritis With Cortisone and Corticotropin, Am. J. Med. **14**:265, 1953.
19. West, H. F., and Newns, G. R.: Cortisone and Rheumatoid Diseases, Lancet **2**:1123, 1953.
20. Weinberger, H. J., discussion of Ogryzlo, M. Diffuse Systemic Rheumatoid Disease, Proc. Ann. Mtg. Amer. Rheum. Assn., 1953, Abstr. Ann. Rheumat. Dis. **12**:324, 1953.
21. O'Brien, D. J., and Storey, G.: Death From Hypersensitivity Due to Phenylbutazone, Brit. M. J. **1**:792, 1954.
22. Slocumb, C. H.: Rheumatic Complaints During Chronic Hypercortisonism and Syndromes During Withdrawal of Cortisone in Rheumatic Patients, Proc. Staff Meet., Mayo Clin. **28**:655, 1953.
23. Steiner, G., Freund, H. A., Leichtentritt, B., and Price, A. E.: Lesions of Skeletal Muscle in Rheumatoid Arthritis, Am. J. Path. **22**:103, 1946.
24. Sokoloff, L., Wilens, S. L., Bunim, J. J., and McEwen, C.: Diagnostic Value of Histologic Lesions of Striated Muscle in Rheumatoid Arthritis, Am. J. M. Sc. **219**:174, 1950.
25. Freund, H. A., Steiner, G., Leichtentritt, B., and Price, A. E.: Peripheral Nerves in Chronic Atrophic Arthritis, Am. J. Path. **18**:865, 1942.
26. Morrison, L. R., Short, C. L., Ludwig, A. O., and Schwab, R. S.: The Neuromuscular System in Rheumatoid Arthritis, Electromyographic and Histologic Observations, Am. J. M. Sc. **214**:33, 1947.
27. Friedenwald, J. S., Wilder, H. C., Maumenee, A. E., Sanders, T. E., Keyes, J. E. L., Hogan, M. J., Owens, W. C., and Owens, E. U.: Ophthalmic Pathology, Philadelphia, 1952, W. B. Saunders Company.
28. Sury, B.: Rheumatoid Arthritis in Children. A Clinical Study, Copenhagen, 1952, Ejnar Munksgaards Forlag.
29. Morgan, W. S.: The Probable Systemic Nature of Mikulicz's Disease and Its Relation to Sjogren's Syndrome, New England J. Med. **251**:5, 1954.
30. Sokoloff, L., Sharp, J. T., and Kaufman, E. H.: The Adrenal Cortex in Rheumatic Disease, Arch. Int. Med. **88**:627, 1951.
31. Pearse, A. G. E.: The Hypophysis in Rheumatoid Arthritis, Lancet **1**:954, 1950.
32. Bennett, W. A.: Histopathological Alterations of Adrenal and Anterior Pituitary Glands in Patients Treated With Cortisone, J. Bone & Joint Surg. **36A**:867, 1954.
33. Hayhoe, G. J., and Smith, D. R.: Plasmacytosis in the Bone Marrow in Rheumatoid Arthritis, J. Clin. Path. **4**:47, 1951.
34. Motulsky, A. G., Weinberg, S., Saphir, O., and Rosenberg, E.: Lymph Nodes in Rheumatoid Arthritis, Arch. Int. Med. **90**:660, 1952.
35. Hutt, M. S. R., Richardson, J. S., and Staffurth, J. S.: Felty's Syndrome. A Report of Four Cases Treated by Splenectomy, Quart. J. Med. **20**:57, 1951.
36. Raven, R. W., Weber, F. P., and Price, L. W.: The Necrobiotic Nodules of Rheumatoid Arthritis. Case in Which the Scalp, Abdominal Wall (Involving Striped Muscle), Larynx, Pericardium (Involving Myocardium), Pleurae (Involving Lungs), and Peritoneum Were Affected, Ann. Rheumat. Dis. **7**:63, 1948.
37. Bevans, M., Nadell, J., Demartini, F., and Ragan, C.: The Systemic Lesions of Malignant Rheumatoid Arthritis, Am. J. Med. **16**:197, 1954.
38. Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M.: Amyloidosis in Rheumatoid Arthritis; a Report of Ten Cases, Am. J. M. Sc. **216**:51, 1948.
39. Fingerman, D. L., and Andrus, F. C.: Visceral Lesions Associated With Rheumatoid Arthritis, Ann. Rheumat. Dis. **3**:168, 1943.
40. Movitt, E. R., and Davis, A. E.: Liver Biopsy in Rheumatoid Arthritis, Am. J. M. Sc. **226**:516, 1953.
41. Tumulty, P. A., and Harvey, A. McG.: The Clinical Course of Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **85**:47, 1949.
42. Ross, S. W., and Wells, B. B.: Systemic Lupus Erythematosus, Am. J. Clin, Path. **23**:139, 1953.
43. Dubois, E. L.: The Effect of the L.E. Cell Test on the Clinical Picture of Lupus Erythematosus Disseminatus, Ann. Int. Med. **38**:1265, 1953.
44. Jessar, R. A., Lamont-Havers, R. W., and Ragan, C.: Natural History of Lupus Erythematosus Disseminatus, Ann. Int. Med. **38**:717, 1953.
45. Svartz, N.: Agglutination With Sensitized Sheep Cells in Rheumatoid Arthritis, J. Am. M. Women's A. **5**:261, 1950.
46. Ball, T.: Sheep Cell Agglutination Test for Rheumatoid Arthritis, Ann. Rheumat. Dis. **11**:97, 1952.
47. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J.: The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, Arch. Int. Med. **43**:571, 1929.
48. Nicholls, E. E., and Stainsby, W. J.: Streptococcal Agglutinins in Infectious Arthritis, J. Clin. Invest. **10**:323, 1931.
49. McEwen, C., Bunim, J. J., and Alexander, R. C.: Bacteriologic and Immunologic Studies in Arthritis. II. Results of Various Immunologic Tests in Different Forms of Arthritis, J. Lab. & Clin. Med. **21**:465, 1936.

50. Dawson, M. H., Olmstead, M., and Boots, R. H.: Agglutination Reactions in Rheumatoid Arthritis. I. Agglutination Reactions With Streptococcus Hemolyticus, J. Immunol. **23**:187, 1932.
51. Wallis, A. D.: Rheumatoid Arthritis. II. Non-specific Serologic Reactions, Am. J. M. Sc. **212**:716, 1946.
52. Waaler, E.: On the Occurrence of a Factor in Human Serum Activating the Specific Agglutination of Sheep Blood Corpuscles, Acta path. et microbiol. scandinav. **17**:172, 1940.
53. Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O.: Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients With Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **68**:1, 1948.
54. Ball, J.: Serum Factor in Rheumatoid Arthritis Agglutinating Sensitised Sheep Red Cells, Lancet **2**:520, 1950.
55. Heller, G., Jacobson, A. S., and Kolodny, M. H.: A Modification of the Hemagglutination Test for Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **72**:316, 1949.
56. Heller, G., Jacobson, A. S., Kolodny, M. H., and Schuman, R. L.: The Hemagglutination Test for Rheumatoid Arthritis. I. An Immunological Analysis of the Factors Involved in the Reaction, J. Immunol. **69**:27, 1952.
57. Heller, G., Jacobson, A. S., Kolodny, M. H., and Kammerer, W. H.: The Hemagglutination Test for Rheumatoid Arthritis. II. The Influence of Human Plasma Fraction II (Gamma Globulin) on the Reaction, J. Immunol. **72**:66, 1954.
58. Ziff, M., Brown, P., and McEwen, C.: Hemagglutination Tests for Rheumatoid Arthritis With Enhanced Sensitivity Using the Euglobulin Fraction, Bull. Rheumat. Dis. **5**:75, 1954.
59. Williams, R. R., Stone, S. S., Jenkins, J., and Bunim, J. J.: Unpublished data.
60. Robinson, A. R., Stulberg, C. S., and Kuyper, A. C.: Identification of the Substance Active in Sheep Cell Agglutination Test for Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **85**:4, 1954.
61. Saroff, H. A., Williams, R. R., and Bunim, J. J.: Unpublished data.
62. Gorrill, R. H., and Hobson, D.: The Agglutinating Property of Complement, J. Path. & Bact. **64**:257, 1952.
63. Hirst, G. K.: The Nature of the Virus Receptors of Red Cells. III. Partial Purification of the Virus Agglutination Inhibitor in Human Plasma, J. Exper. Med. **89**:223, 1949.
64. Tamm, I., and Horsfall, F. L.: A Mucoprotein Derived From Human Urine Which Reacts With Influenza, Mumps, and Newcastle Disease Viruses, J. Exper. Med. **95**:71, 1952.
65. Hoyt, R. E., and Zwicker, H.: The Role of Enzyme in Reversible Agglutination of Red Cells, J. Immunol. **71**:325, 1953.
66. Pike, R. M., Sulkin, S. E., and Coggeshall, H. C.: Serological Reactions in Rheumatoid Arthritis. I. Factors Affecting the Agglutination of Sensitized Sheep Erythrocytes in Rheumatoid-Arthritis Serum, J. Immunol. **63**:441, 1949.
67. Alexander, R., and de Forest, G. K.: The Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis, Am. J. Med. **16**:191, 1954.
68. Svartz, N., and Schlossmann, K.: Agglutination of Sensitized Sheep Erythrocytes by Cold Precipitable Serum Substances in Rheumatoid Arthritis, Acta med. scandinav. **146**:313, 1953.
69. Brown, R., Bunim, J. J., and McEwen, C.: Differential Sheep-Cell Agglutination Test in Rheumatoid Arthritis, Ann. Rheumat. Dis. **8**:299, 1949.
70. Jawetz, E., and Hook, E. V.: Differential Sheep Cell Agglutination in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **70**:650, 1949.
71. Miller, J. E., Lynch, E. R., and Lansbury, J.: Failure of Sensitized Sheep Cell Agglutination to Clarify the Diagnosis of Rheumatic Disease, J. Lab. & Clin. Med. **34**:1216, 1949.
72. Sulkin, S. E., Pike, R. M., and Coggeshall, H. C.: Specificity of Differential Sheep Cell Agglutination Test in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **70**:475, 1949.
73. Dordick, J. R., and Wasserman, M. M.: The Differential Sheep Cell Agglutination Cell Test in Arthritis, Am. J. Clin. Path. **20**:526, 1950.
74. Svartz, N., and Schlossmann, K.: The Agglutinating Factor for Sensitized Sheep Erythrocytes in Serum and Joint Fluid From Rheumatoid Arthritis Patients, Ann. Rheumat. Dis. **9**:377, 1950.
75. Wager, O.: On the Factor Producing Agglutination of Sensitized Red Cells and Its Relation to the Agglutination of Hemolytic Streptococci in Rheumatoid Arthritis Sera, Ann. med. exper. et biol. Fenniae **28**:Suppl. 8, 1950.
76. Scott, F. E. T.: The Differential Sheep-Cell Agglutination Test in Rheumatoid Arthritis, Lancet **1**:392, 1952.
77. Pike, R. M., Sulkin, S. E., Coggeshall, H. C., and Burdette, R. I.: Serological Reaction in Rheumatoid Arthritis. IV. Persistence of the Serum Factor Which Agglutinates Sensitized Sheep Cells, J. Lab. & Clin. Med. **41**:880, 1953.

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78. Svartz, N., and Schlossmann, K.: The Hemagglutination Test With Sensitized Sheep Cells in Rheumatoid Arthritis and Some Other Diseases, Acta med. scandinav. **142**:420, 1952.
79. Ragan, C., Grokoest, A. W., and Boots, R. H.: Effect of Adrenocorticotropic Hormone (ACTH) on Rheumatoid Arthritis, Am. J. Med. **7**:741, 1949.
80. Svartz, N.: The Effect of ACTH on the Agglutination With Sensitized Red Sheep Cells in Rheumatoid Arthritis, Acta med. scandinav. **246**:240, 1950.
81. Robinson, W. D., French, A. J., and Duff, I. F.: Polyarteritis in Rheumatoid Arthritis (in Transactions of Am. Rheum. Assoc.), Ann. Rheumat. Dis. **12**:323, 1953.
82. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions: A Study in Clinical Physiology, Arch. Int. Med. **85**:545, 1950.
83. Norcross, B. M., Lockie, L. M., Constantine, A. G., Talbott, J. H., and Stein, R. H.: The Effect of Cortone and ACTH on the Histopathologic Lesions of Rheumatoid Arthritis, Ann. Int. Med. **36**:751, 1952.
84. Bunim, J. J., Ziff, M., and McEwen, C.: Evaluation of Prolonged Cortisone Therapy, Am. J. Med. (In press.)
85. Copeman, W. S. C., Savage, O., Dodds, C., Glyn, J. H., and Fearnley, M. E.: Management of Rheumatoid Arthritis With Prolonged Cortisone Administration, Brit. M. J. **1**:1109, 1954.
86. Engleman, E. P., Krupp, M. A., Saunders, W. W., Wilson, L. E., and Fredell, E. W.: Rheumatoid Arthritis—An Evaluation of Long-term Treatment With Cortisone, California Med. **80**:369 (May) 1954.
87. Bunim, J. J., Ziff, M., and McEwen, C.: Cortisone Therapy in Rheumatoid Arthritis: A Four-Year Appraisal, Bull. Rheumat. Dis. **5**:73 (Sept.) 1954.
88. Ward, L. E., Hench, P. S., Slocumb, C. H., and Polley, H. F.: Comparative Effects of Hydrocortisone (Free Alcohol), Hydrocortisone Acetate and Cortisone Acetate in Rheumatoid Arthritis (in Transactions of Am. Rheum. Assoc.), Ann. Rheumat. Dis. **12**:327, 1953.
89. Boland, E. W.: Antirheumatic Effects of Hydrocortisone (Free Alcohol), Hydrocortisone Acetate, and Cortisone (Free Alcohol) as Compared With Cortisone Acetate: Results From Oral Administration in Patients With Rheumatoid Arthritis, Brit. M. J. **1**:559, 1952.
90. Short, C. L., and Bauer, W.: The Course of Rheumatoid Arthritis in Patients Receiving Simple Medical and Orthopedic Measures, New England J. Med. **238**:142, 1948.
91. Hench, P. S., and Ward, L. E.: Rheumatoid Arthritis and Other Rheumatic or Articular Diseases, chap. 3 in Lukens, F. D. W.: Medical Uses of Cortisone, New York, 1954, Blakiston Company.
92. Robinson, W. D., et al.: Rheumatism and Arthritis: Review of American and English Literature of Recent Years, Ann. Int. Med. **39**:498, 1953.
93. Cohen, H., Bywaters, E. G. L., Copeman, W. S. C., Dodds, C., Duthie, J. J. R., Hill, A. B., Osmond-Clarke, H., Prunty, F. T. G., Reid, J., West, H. F., Kellgren, J. H., and Sanderson, W. A.: A Comparison of Cortisone and Aspirin in the Treatment of Early Cases of Rheumatoid Arthritis, Brit. M. J. **1**:1223, 1954.
94. Hollander, J. L.: Intra-articular Hydrocortisone in the Treatment of Arthritis, Ann. Int. Med. **39**:735, 1953.
95. Hollander, J. L.: Intra-articular Injection of Hydrocortisone, chapt. 18 in Comroe, B. I.: Arthritis and Allied Conditions, ed. 5, Philadelphia, 1953, Lea & Febiger.
96. Ziff, M., Scull, E., Ford, D., McEwen, C., and Bunim, J. J.: Effects in Rheumatoid Arthritis of Hydrocortisone and Cortisone Injected Intra-articularly, Arch. Int. Med. **90**:774, 1952.
97. Bilka, P. J.: Intra-articular Use of Hydrocortisone in Rheumatic Diseases, Minnesota Med. **35**:938, 1952.
98. Hashtan, H. A.: Hydrocortisone (Compound F) in Arthritic Joints, Harper Hosp. Bull. **10**:143, 1952.
99. Berry, W. C., and Benson, J. F.: Hydrocortisone in Rheumatoid Arthritis, U. S. Armed Forces M. J. **4**:99, 1953.
100. Gewalli, Nils: Experiences of Prolonged Cortisone and ACTH Treatment in Rheumatoid Arthritis, Acta med. scandinav. **148**:291, 1954.
101. Davison, S.: Experiences in the Treatment of Rheumatoid Arthritis With Cortisone, New York J. Med. **51**:2393, 1951.
102. Copeman, W. S., Savage, O., Bishop, P. M. F., Dodds, E. C., Kellie, A. E., Stewart, J. W., Glyn, J. H. H., Henly, A. A., and Tweed, J. M.: Observations on Prolonged Cortisone Administration in Rheumatoid Arthritis, Brit. M. J. **1**:397, 1952.
103. Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S.: Clinical Effects of Cortisone Administered Orally to Patients With Rheumatoid Arthritis, Proc. Staff Meet., Mayo Clin. **26**:361, 1951.
104. Boland, E. W., and Headley, N. E.: Results of Long-Continued Cortisone Administration in Rheumatoid Arthritis, California Med. **74**:416, 1951.

OL.
1
955

105. Boland, E. W.: Prolonged Uninterrupted Cortisone Therapy in Rheumatoid Arthritis, Brit. M. J. **2**:191, 1951.
106. Fischer, F., and Gillmor, C. S.: ACTH and Cortisone in Rheumatoid Arthritis; a Follow-up Study of the Clinical Effect in Thirty-four Cases, J. Missouri M. A. **49**:123, 1952.
107. McGavack, T. H.: ACTH, Cortisone, and Pregnenolone in Arthritis and Allied Disease, Geriatrics **7**:99, 1952.
108. Holbrook, W. P., Hill, D. F., Stephens, C. A. L., Jr., and Kent, L. J.: The Use of Adrenocorticotropic Hormone (ACTH) and Cortisone in Rheumatoid Arthritis, Ann. West. Med. & Surg. **5**:1000, 1951.
109. Norcross, B. M., Lockie, L. M., and Talbott, J. H.: Evaluation of Steroids in Rheumatoid Arthritis, New York J. Med. **51**:1031, 1951.
110. Freyberg, R. H., Traeger, C. H., Patterson, M., Squires, W., Adams, C. H., and Stevenson, C.: Problems of Prolonged Cortisone Treatment for Rheumatoid Arthritis; Further Investigations, J.A.M.A. **147**:1538, 1951.
111. Ragan, C.: Undesirable Side-Effects, Withdrawal Symptoms and Contraindications of Use of Cortisone and ACTH, Bull. Rheumat. Dis. **1**:5, 1950.
112. Clark, W. S., Tonning, H. O., Kulka, J. P., and Bauer, W.: Observations on the Use of Cortisone and ACTH in Rheumatoid Arthritis, New England J. Med. **249**:635, 1953.
113. Homburger, F., and Bonner, C. D.: Therapeutic Studies With ACTH and Cortisone. I. Long-Term Observations in Rheumatoid Arthritis and Other Diseases, Geriatrics **8**:385, 1953.
114. Rosenberg, I. N., Cleroux, A. P., Raben, M. S., Payne, R. W., and Astwood, E. B.: Clinical Evaluation of Corticotropin Therapy, Arch. Int. Med. **88**:211, 1951.
115. Salassa, R. M., Bennett, W. A., Keating, F. R., Jr., and Sprague, R. G.: Postoperative Adrenal Cortical Insufficiency: Occurrence in Patients Previously Treated With Cortisone, J.A.M.A. **152**:1509, 1953.
116. Forestier, J., Certonciny, A., and Jacqueline, F.: Quelques précisions sur les contra-indications de la cortisone et de l'ACTH dans les rhumatismes inflammatoires, Rev. rhum. **18**:184, 1951; Injections intra-articulaire de cortisone et d'ACTH dans les rhumatismes inflammatoires, Rev. rhum. **18**:207, 1951.
117. Fraser, C. G., Preuss, F. S., and Bigford, W. D.: Adrenal Atrophy and Irreversible Shock Associated With Cortisone Therapy, J.A.M.A. **149**:1542, 1952.
118. Borman, M. C., and Schmallenberg, H. C.: Suicide Following Cortisone Treatment, J.A.M.A. **146**:337, 1951.
119. Mowbray, J.: Cortisone in the Treatment of Rheumatoid Arthritis in Children, J. Irish M. A. **31**:348, 1952.
120. Glyn, J. H.: Case Reports From a Long-Term Series on Cortisone, West London Hosp. Rep., p. 6, 1952.
121. Hench, P. S., Slocumb, C. H., Polley, H. F., and Kendall, E. C.: Effect of Cortisone and Pituitary Adrenocorticotropic Hormone (ACTH) on Rheumatic Diseases, J.A.M.A. **144**:1327, 1950.
122. Steinbrocker, O., Berkowitz, S., Carp, S., Ehrlich, M., Elkind, M., Silver, M., and Spitzer, N.: ACTH and Cortisone as Therapeutic Agents in Arthritis and Some Locomotor Disorders, Bull. New York Acad. Med. **27**:560, 1951.
123. Margolis, H. M., and Caplan, P. S.: Effects of Pituitary Adrenocortiocotropic Hormone (ACTH) in Rheumatoid Arthritis, J.A.M.A. **145**:382, 1951.
124. Bilka, P. J.: New Developments in the Use of Cortisone in Rheumatoid Arthritis, Minnesota Med. **34**:1088, 1951.
125. Price, A. E., Reveno, W. S., Lightbody, J. J., Vonder Heide, E. C., Kashtan, H. A., and Corrigan, K. E.: Observations on the Use of Cortisone and Corticotropin in Rheumatoid Arthritis, J. Michigan M. Soc. **51**:1183, 1952.
126. Achari, G., Mukopadhaya, B., and Sengupta, P.: Rheumatoid Arthritis Treated With Irgapyrin; Analysis of 20 Cases, Ann. Rheumat. Dis. **12**:32, 1953.
127. Bach, F.: Butazolidine, Lancet **2**:92, 1952.
128. Benstead, J. G.: Deaths of Two Patients Treated by Phenylbutazone, Brit. M. J. **1**:711, 1953.
129. Brandwein, S.: Agranulocytosis Following Phenylbutazone (Butazolidin), New York J. Med. **53**:1577, 1953.
130. Cudkowicz, L., and Jacobs, J. H.: Phenylbutazone (Butazolidine) in the Treatment of Chronic Arthritis, Lancet **1**:223, 1953.
131. Currie, J. P.: Treatment of Rheumatoid Arthritis With Butazolidine, Lancet **2**:15, 1952.
132. Currie, J. P., Brown, R. A., and Will, G.: Observations on the Treatment of Rheumatoid Arthritis With Butazolidin, Ann. Rheumat. Dis. **12**:88, 1953.
133. Davies, H. R., Barter, R. W., Gee, A., and Hirson, C.: Observations on the Use of "Butazolidin" in Arthritis, Brit. M. J. **2**:1392, 1952.
134. Dilling, N. V.: Fatal Agranulocytosis and Gastric Ulceration Due to Phenylbutazone, Lancet **1**:1230, 1953.
135. Etess, A. D., and Jacobson, A. S.: Fatality Due to Agranulocytosis Following Use of Phenylbutazone (Butazolidin), J.A.M.A. **151**:639, 1953.

VOL
1
195

136. Freeland, D., Storey, G., and Thompson, M.: Treatment of Rheumatoid Arthritis With Phenylbutazone, Lancet **1**:1227, 1953.
137. Gillhespy, R. O.: Phenylbutazone, Brit. M. J. **2**:287, 1953.
138. Granirer, L. W.: Untoward Effects of Phenylbutazone (Butazolidin) (Correspondence), J.A.M.A. **150**:1332, 1952.
139. Hart, F. O., and Johnson, A. M.: Butazolidine, Lancet **2**:587, 1952.
140. Kuzell, W. C., Schaffarzick, R. W., Brown, B., and Mankle, E. A.: Phenylbutazone (Butazolidin) in Rheumatoid Arthritis and Gout, J.A.M.A. **149**:729, 1952.
141. Kuzell, W. C., and Schaffarzick, R. W.: Phenylbutazone (Butazolidin) and Butapyrin; a Study of Clinical Effects in Arthritis and Gout, California Med. **77**:319, 1952.
142. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Gaudin, G., and Mankle, E. A.: Phenylbutazone: Further Clinical Evaluation, Arch. Int. Med. **92**:646, 1953.
143. Kidd, E. G., Boyce, K. C., and Freyberg, R. H.: Clinical Studies of Phenylbutazone (Butazolidin) and Butapyrin (Irgapyrin) in Rheumatoid Arthritis, Rheumatoid Spondylitis and Gout, Ann. Rheumat. Dis. **12**:20, 1953.
144. Krainin, P.: Gastric Ulcer With Massive Hemorrhage Following Use of Phenylbutazone, J.A.M.A. **152**:31, 1953.
145. Leonard, J. C.: Toxic Effects of Phenylbutazone With Special Reference to Disorders of the Blood, Brit. M. J. **1**:1311, 1953.
146. Lorton, G. E., LeVay, D., and Wilson, P.: Butazolidine, Lancet **2**:682, 1952.
147. MacKnight, J. C., Irby, R., and Toone, E. C., Jr.: Phenylbutazone in Management of Rheumatoid Arthritis, Rheumatoid Spondylitis and Gouty Arthritis, Geriatrics **9**:111, 1954.
148. Mason, R. M.: Comparative Effects of ACTH and Butazolidin in Rheumatoid Arthritis, Ann. Rheumat. Dis. **12**:82, 1953.
149. Nassim, J. R., and Pillington, T.: Toxic Effects of Phenylbutazone, Brit. M. J. **1**:1310, 1953.
150. Patterson, R. M., Benson, J. F., and Schoenberg, P. L.: Clinical Evaluation of Phenylbutazone, U. S. Armed Forces M. J. **4**:109, 1953.
151. Peebles Brown, R. A., and Currie, J. P.: Butazolidine, Lancet **2**:682, 1952.
152. Pierik, M. G.: Clinical Use of Phenylbutazone, a Potent Antirheumatic Agent; Report of Its Effectiveness in 4 Cases, Rhode Island M. J. **36**:196, 1953.
153. Raffensperger, E. C.: Multiple Gastric Ulcers Occurring During Phenylbutazone Therapy, J.A.M.A. **152**:30, 1953.
154. Shields, W. E., Adamson, N. E., Jr., and MacGregor, J. B.: Peptic Ulcer Perforation Following Administration of Phenylbutazone, J.A.M.A. **152**:28, 1953.
155. Shulman, J.: Butazolidin, Lancet **2**:887, 1952.
156. Smith, C. H., and Kunz, H. G.: Butazolidin in Rheumatoid Disorders; a Preliminary Report, J. M. Soc. New Jersey **49**:306, 1952.
157. Snow, W. G.: Phenylbutazone: An Evaluation of Its Use, California Med. **79**:211, 1953.
158. Solomon, R. M.: Correspondence, Brit. M. J. **1**:159, 1953.
159. Stanfield, A. B., Brodie, E. C., and Yeoman, E. E.: Butazolidin Plasma Concentration and Urinary Excretion in Normal Individuals and in Patients With Rheumatoid Spondylitis, Proc. Soc. Exper. Biol. & Med. **83**:254, 1953.
160. Steinberg, C. L., Bohrod, M. G., and Roodenburg, A. I.: Agranulocytosis Following Phenylbutazone (Butazolidin) Therapy: Report of a Fatal Case, J.A.M.A. **152**:33, 1953.
161. Steinbrocker, O., Berkowitz, S., Carp, S., Ehrlich, M., and Elkind, M.: Therapeutic Observations on Butazolidin (Phenylbutazone) in Some Arthritides and Related Conditions, Ann. Rheumat. Dis. **11**:296, 1952.
162. Steinbrocker, O., Berkowitz, S., Ehrlich, M., Elkind, M., and Carp, S.: Phenylbutazone Therapy of Arthritis and Other Painful Musculoskeletal Disorders, J.A.M.A. **150**:1087, 1952.
163. Stephens, C. A. L., Jr., Yeoman, E. E., Holbrook, W. P., Hill, D. F., and Goodwin, W. L.: Benefits and Toxicity of Phenylbutazone (Butazolidin) in Rheumatoid Arthritis, J.A.M.A. **150**:1084, 1952.
164. Strazza, J. A., Jr., and Ressetar, M.: Butazolidin in the Treatment of Arthritis; Clinical Studies With Phenylbutazone, J. M. Soc. New Jersey **50**:333, 1953.
165. Werblow, S. C., and Neber, J.: Agranulocytosis Following Phenylbutazone Therapy, J.A.M.A. **151**:1286, 1953.
166. Wilkinson, E. L., and Brown, H.: The Effect of Butazolidin (Phenylbutazone) on Water and Electrolyte Excretion, Am. J. M. Sc. **225**:153, 1953.
167. Deaths Due to Butazolidin, Brit. M. J. **2**:1427, 1952.
168. Hazards of Phenylbutazone Treatment, Lancet **1**:1236, 1953.
169. Death Due to Butazolidin, Lancet **1**:192, 1953.
170. Nathan, D. A., Meitus, M. L., Capland, L., and Lev, M.: Death Following Phenylbutazone (Butazolidin) Therapy: Report of a Case, Ann. Int. Med. **39**:1096, 1953.

OL.
1
955

171. Brodie, B. B., Lowman, E. W., Burns, J. J., Lee, P. R., Chenkin, T., Goldman, A., Weiner, M., and Steele, J. M.: Observations on the Antirheumatic and Physiologic Effects of Phenylbutazone (Butazolidin) and Some Comparisons With Cortisone, Am. J. Med. **16**:181, 1954.
172. Kuzell, W. C.: Phenylbutazone (Butazolidin), Bull. Rheumat. Dis. **3**:23, 1952.
173. Bunim, J. J.: Cortisone and Phenylbutazone (Butazolidin): Similarities and Differences, GP **8**:40, 1953.
174. Hersperger, W. G.: Gold Therapy for Rheumatoid Arthritis: A Current Evaluation, Ann. Int. Med. **36**:571, 1952.
175. Margolis, H. M., and Caplan, P. S.: Chrysotherapy in Rheumatoid Arthritis, Rheumatism **6**:26, 1950.
176. Neudorff, L. G.: Chrysotherapy in Rheumatoid Arthritis, J. Missouri M. A. **47**:172, 1950.
177. Nyström, G.: Gold Treatment of Rheumatoid Arthritis at Asö and at Södersjukhus (762 Treatments) in 1932-46, Rheumatism **6**:174, 1950.
178. Freyberg, R. H.: Present Status of Gold Therapy for Rheumatoid Arthritis, J.A.M.A. **143**:418, 1950.
179. Adams, C. H., and Cecil, R. L.: Gold Therapy in Early Rheumatoid Arthritis, Ann. Int. Med. **33**:163, 1950.
180. Freyberg, R. H., Block, W. D., and Levey, S.: Metabolism, Toxicity and Manner of Action of Gold Compounds Used in the Treatment of Arthritis. I. Human Plasma and Synovial Fluid Concentration and Urinary Excretion of Gold During and Following Treatment With Gold Sodium Thiomalate, Gold Sodium Thiosulfate and Colloidal Gold Sulfide, J. Clin. Invest. **20**:401, 1941.
181. Freyberg, R. H.: Gold Salts in the Treatment of Chronic Arthritis: Metabolic and Clinical Studies, Proc. Staff Meet., Mayo Clin. **17**:534, 1942.
182. Lawrence, J. S.: Factors in Gold Dosage and Toxicity in Rheumatoid Arthritis, Ann. Rheumat. Dis. **12**:129, 1953.
183. Bollet, A. J., and Bunim, J. J.: The Importance of Serial X-rays in the Evaluation of Treatment of Rheumatoid Arthritis, M. Clin. North America. (In press.)
184. Ragan, C.: Rheumatoid Arthritis: The Natural History of the Disease and Its Management, Bull. New York Acad. Med. **27**:63, 1951.
185. Thompson, H. E., and Rowe, H. J.: Cortisone and Gold Therapy in Chronic Rheumatoid Arthritis, Ann. Int. Med. **36**:992, 1952.
186. Archer, B. H.: Hepatitis Following Gold Therapy, J.A.M.A. **144**:782, 1950.
187. Archer, B. H.: Gold Salt Therapy, Minimal Liver Damage, and Remission of Rheumatoid Arthritis, New York J. Med. **52**:601, 1952.
188. Batterman, R. C.: Treatment of Rheumatoid Arthritis With Aurothioglycanide (Lauron), J.A.M.A. **152**:1013, 1953.
189. Doyle, J. B., and Cannon, E. F.: Severe Polyneuritis Following Gold Therapy for Rheumatoid Arthritis, Ann. Int. Med. **33**:1468, 1950.
190. Gilbert, J. T., Jr., and Moore, F. H.: Gold Therapy in Rheumatoid Arthritis, J. Kentucky M. A. **48**:308, 1950.
191. McMahon, J. M.: Toxic Reaction From Gold Appearing During ACTH Administration; Report of a Case, New Orleans M. & S. J. **104**:674, 1952.
192. Merliss, R. R., Axelrod, B., Fineberg, J., and Melnik, M.: Clinical Evaluation of Aurothioglycolanilide (Lauron-Endo) in Rheumatoid Arthritis, Ann. Int. Med. **35**:352, 1951.
193. Nugent, T. E., Nugent, F. W., and O'Neil, F. B.: Gold Therapy in Rheumatoid Arthritis in Private Practice, Canad. M.A.J. **68**:225, 1953.
194. Snorrason, E.: Rheumatoid Arthritis, Sanocrysin Treatment and Prognosis, Acta med. scandinav. **142**:249, 1952.
195. Peebles Brown, R. A., and Currie, J. P.: Observations on Gold Therapy in Rheumatoid Arthritis, Brit. M.J. **1**:916, 1953.
196. Egelius, N., Hävermark, N. G., and Nyström, G.: Late Results of Gold Therapy in Rheumatoid Arthritis, Nord. med. **45**:968, 1951.
197. Egelius, N., Hävermark, N. G., and Nyström, G.: Late Results of Gold Treatment in Rheumatoid Arthritis, Ann. Rheumat. Dis. **11**:17, 1952.
198. Schwartz, S., Blain, H. R., Geiger, H. B., and Hartung, E. F.: Investigation of Use of Aurothioglyconide (Lauron) in Rheumatoid Arthritis, J.A.M.A. **154**:1263, 1954.
199. Lewin, E., and Wassen, E.: Effect of Combined Injections of Deoxycortone Acetate and Ascorbic Acid on Rheumatoid Arthritis, Lancet **2**:993, 1949.
200. Le Vay, D., and Loxton, G. E.: Clinical Observations With Deoxycortone and Ascorbic Acid, Lancet **1**:209, 1950.
201. Newman, M. K.: Desoxycorticosterone Acetate and Ascorbic Acid in the Management of Rheumatoid Arthritis, Ann. Rheumat. Dis. **9**:404, 1950.
202. McKendry, J. B. R., Schaffenburg, C. A., and McCullagh, E. P.: Combined Administration of Desoxycorticosterone Acetate and Ascorbic Acid. I. Clinical Results in Rheumatoid Arthritis and Laboratory Studies, Arch. Int. Med. **87**:190, 1951.

VOL. 1 1955

203. Bergman, B., and Kinberger, F. R.: A Case Report of the Use of Combined DOCA and Ascorbic Acid in a 12-year-old Child With Rheumatoid Arthritis, J. Pediat. **37**:774, 1950.
204. Wingfield, W. L., Toone, E. C., Jr., Williams, J. P., and Becker, E.: Evaluation of Certain New Therapeutic Measures in the Management of Rheumatoid Arthritis, Virginia M. Monthly **78**:539, 1951.
205. Currie, J. P., and Will, G.: Treatment of Rheumatoid Arthritis With Deoxycortone and Vitamin C, Lancet **1**:708, 1950.
206. Littman, D. S., Stockdale, R. H., and Williamson, G. R.: Desoxycorticosterone Acetate and Ascorbic Acid in the Treatment of Rheumatoid Arthritis, Arch. Int. Med. **87**:707, 1951.
207. Quin, C. E., Mason, R. M., and Knowelden, J.: Clinical Assessment of Rapidly Acting Agents in Rheumatoid Arthritis, Brit. M. J. **2**:810, 1950.
208. Bywaters, E. G. L., and Dixon, A. St. J.: Deoxycortone and Ascorbic Acid in the Treatment of Rheumatoid Arthritis, Lancet **1**:951, 1950.
209. MacLean, K. S.: Deoxycortone Acetate and Ascorbic Acid in Rheumatoid Arthritis, Lancet **1**:444, 1951.
210. Margolis, H. M., and Caplan, P. S.: The Effect of Some Steroids (Testosterone Propionate, Desoxycorticosterone Acetate and Ascorbic Acid, and 21-Acetoxy-delta-5-pregnenolone, Artisone Acetate, Wyeth) in Rheumatoid Arthritis, Ann. Int. Med. **34**:61, 1951.
211. Dordick, J. R., Rechtschaffen, J. S., and Alexander, S.: Desoxycorticosterone Acetate and Ascorbic Acid in Arthritis, New York J. Med. **51**:1413, 1951.
212. Kling, D. H.: Desoxycorticosterone Acetate and Ascorbic Acid Injections in Rheumatoid Arthritis, J.A.M.A. **143**:791, 1950.
213. Kersley, G. D., Mandel, L., and Jeffrey, M. R.: Steroid Therapy in Rheumatoid Arthritis, Lancet **1**:703, 1950.
214. Davison, S.: Deoxycortone and Ascorbic Acid, Lancet **2**:770, 1950.
215. Clark, W. S., Tonning, H. O., Blais, J. A., and Bauer, W.: Effects of Some 11-Desoxysteroids in Rheumatoid Arthritis, Ann. Rheumat. Dis. **10**:487, 1951.
216. Terry, L. L., and London, F.: Desoxycortone and Ascorbic Acid, Lancet **2**:771, 1950.
217. Lefkovits, A. M., and Schupbach, H. J.: Effects of "Artisone" Acetate and Cortisone in Patients With Rheumatoid Arthritis, Arch. Int. Med. **88**:201, 1951.
218. Freeman, H., Pincus, G., Bachrach, S., Johnson, C. W., McCabe, G. E., and MacGilpin, H. H., Jr.: Oral Steroid Medication in Rheumatoid Arthritis, J. Clin. Endocrinol. **10**:1523, 1950.
219. Freeman, H., Pincus, G., Johnson, C. W., Bachrach, S., McCabe, G. E., and MacGilpin, H.: Therapeutic Efficacy of Δ^5—Pregnenolone in Rheumatoid Arthritis: Preliminary Observations, J.A.M.A. **142**:1124, 1950.
220. Seifter, J., Warter, P. J., and Fitch, D. R.: Preliminary Observations on the Antiarthritic Effect of 21-Acetoxypregnenolone, Proc. Soc. Exper. Biol. & Med. **73**:131, 1950.
221. Davison, R., Koets, P., Snow, W. G., and Gabrielson, L. G.: Effects of Delta 5 Pregnenolone in Rheumatoid Arthritis, Arch. Int. Med. **85**:365, 1950.
222. Stock, J. P. P., and McClure, E. C.: Pregnenolone in the Treatment of Rheumatoid Arthritis, Lancet **2**:125, 1950.
223. Guest, C. M., Kammerer, W. H., Cecil, R. L., and Berson, S. A.: Epinephrine Pregnenolone and Testosterone in the Treatment of Rheumatoid Arthritis, J.A.M.A. **143**:338, 1950.
224. Rawls, W. B., and Ancona, V. C.: Pregnenolone: Preliminary Report on Pregnenolone Acetate and Acetoxypregnenolone in Arthritis and Soft Tissue Rheumatism, New York J. Med. **51**:1167, 1951.
225. Myers, G. N.: Pregnenolone in the Treatment of Rheumatoid Arthritis, Ann. Rheumat. Dis. **10**:32, 1951.
226. Myers, G. N., and Ross, D. N.: Further Observations on the Use of Pregnenolone in Rheumatoid Arthritis, Ann. Rheumat. Dis. **10**:432, 1951.
227. Higgins, A. R., Jones, R. E., Jr., and Smith, T. W. D.: The Clinical Effects of Delta 5 Pregnenolone in Rheumatoid Arthritis, U. S. Armed Forces M. J. **2**:1717, 1951.
228. Dordick, J. R., Ehrlich, M. E., Alexander, S., and Kissin, M.: Pregnenolone in Rheumatoid Arthritis, New England J. Med. **244**:324, 1951.
229. Brugsch, H. G., and Manning, R. A.: A Comparative Study of Pregnenolone, 21-acetoxypregnenolone and ACTH, New England J. Med. **244**:628, 1951.
230. Davis, J. S., Jr., and Bartfeld, H.: 21-Acetoxypregnenolone in the Treatment of Rheumatoid Arthritis, New York J. Med. **51**:1832, 1951.
231. Terry, L. L., and London, F.: Effects of Reichstein's Compound S Pregnenetriolone Acetate, and 17-Alpha Hydroxyprogesterone in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **73**:251, 1950.
232. Vignos, P. J., Jr., and Dorfman, R. I.: Effect of Large Doses of Progesterone in Rheumatoid Arthritis, Am. J. M. Sc. **222**:29, 1951.
233. Kyle, L. H., and Crain, D. C.: The Clinical and Metabolic Effects of Progesterone and Anhydrohydroxyprogesterone in Rheumatoid Arthritis, Ann. Int. Med. **32**:878, 1950.

234. Alexander, W. R. M., and Duthie, J. J. R.: Progesterone in the Treatment of Rheumatoid Arthritis: A Clinical Trial in 5 Cases, Lancet **1**:297, 1950.
235. Kersley, G. D., and Mandel, L.: Steroid Therapy in Rheumatoid Arthritis; a Further Report, Lancet **1**:1153, 1950.
236. Margolis, H. M., and Caplan, P. S.: The Effect of Some Steroids (Testosterone Propionate) Desoxycorticosterone Acetate and Ascorbic and 21-Acetoxy-delta-5-Pregnenolone, Artisone Acetate, Wyeth in Rheumatoid Arthritis, Ann. Int. Med. **34**:61, 1951.
237. Granirer, L. W.: A Study of the Albumin and Globulin Content in Postpartum Plasma and Its Use in Rheumatoid Arthritis, Science **111**:204, 1950.
238. Granirer, L. W.: A Study of the Lipids in Postpartum Plasma: Its Use in Rheumatoid Arthritis, Surg., Gynec. & Obst. **91**:591, 1950.
239. Granirer, L. W.: ACTH and Cortical Steroids in Postpartum Plasma: Preliminary Report, New York J. Med. **51**:2767, 1951.
240. Granirer, L. W.: Postpartum Plasma in Rheumatoid Arthritis and in Patients Resistant to Cortisone and ACTH, Ann. Rheumat. Dis. **10**:490, 1951.
241. Norcross, B. M., discussion of Granirer, L. W.: Ann. Rheumat. Dis. **10**:490, 1951.
242. Neustadt, D. H., Geiger, J., and Steinbrocker, O.: Effect of Post-partum Plasma in Rheumatoid Arthritis, Ann. Rheumat. Dis. **13**:131, 1954.
243. Aronson, W., Levy, F., Besen, L. J., and Leff, M.: Placental Serum Therapy for Rheumatoid Arthritis, Am. J. M. Sc. **223**:144, 1952.
244. Simson, J., and Bunim, J. J.: Effect of Placental "Serum" in Rheumatoid Arthritis, Ann. Rheumat. Dis. **11**:204, 1952.
245. Spielberg, M.: Placental Blood Serum in the Treatment of Rheumatoid Arthritis; Preliminary Report, Arch. Int. Med. **91**:315, 1953.
246. Lansbury, John: Pregnancy and Rheumatoid Arthritis, Bull. Rheumat. Dis. **4**:38, 1953.
247. Haydu, G. G., and Haydu, B. W.: The Short-term Effect of Pitressin in Rheumatoid Arthritis, Am. J. M. Sc. **223**:1, 1952.
248. Ragan, C., Demartini, F., Lamont-Havers, R., Jessar, R. A., Vaillan-Court, D., and Grokoest, A. W.: A Critical Appraisal of Current Therapy in Rheumatoid Arthritis With Special Reference to ACTH and Cortisone, Bull. New York Acad. Med. **28**:493, 1952.

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Editorials

DIAPHRAGMATIC BREATHING IN PULMONARY EMPHYSEMA

Although symptomatic improvement in pulmonary emphysema has been reported following the use of the breathing and postural exercises advocated by Hofbauer[1] and Heckscher,[2] the methodical use of training in diaphragmatic breathing has not been generally adopted. Quantitative physiologic data which offer a basis for the clinical benefit obtained have been elusive, and tests such as the vital capacity and maximal minute ventilation have shown no change even when patients themselves are subjectively better.[3] Certain measurements of respiratory function are, however, available which support the value of attempts to institute diaphragmatic respiration in patients with pulmonary emphysema and allied chronic respiratory diseases, such as bronchial asthma and bronchiectasis, in which not only impaired diffusion but impaired bronchial drainage play a role in the production of dyspnea.

Chronic pulmonary emphysema has been referred to as hypertrophic or vesicular emphysema characterized by enlargement of the alveoli; and the diffuse, obstructive type produced by the presence of bronchial constriction and retarded expiratory air flow. The role of decreased pulmonary elasticity in the development of the symptoms of this disease has been emphasized by Christie.[4] He related the characteristic impairment of diffusion of oxygen and carbon dioxide in pulmonary emphysema to the earlier ventilation of diseased or bullous areas than of the more normal alveolar structures. A variable part of the tidal air was thus wasted on regions of the lungs poorly equiped with the functioning alveolar membrane and capillary blood supply. Narrowing of the diameter of the bronchi and the imposition of expiratory check-valve mechanisms are now believed to play an important role in promoting distention and irregular ventilation of the alveoli. The impairment in traction of the lung on the bronchial walls also tends to decrease the patency of the bronchiolar airway. However, an earlier filling of the more bullous areas is a limiting factor in gas exchange.[5]

The volume response to various inspiratory pressures has been shown to be diminished, especially when the lungs of patients with emphysema are distended, a phenomenon described under various terms: "lung tension," "compliance," and "lung pressure." Since the decreased tendency of the inflated lungs to expand is considered, from the viewpoint of physical terminology, increased "elasticity," confusion has been aroused in discussions of the earlier concept of impairment in lung elasticity. For the purposes of this discussion, the tendency of the pulmonary parenchyma to recoil, that is, the lung pressure, will be considered a negative pressure which tends to decrease the volume of the thorax and elevate the diaphragm. This tendency of pulmonary tissue to contract is now thought to exert a more important function in maintaining traction of the

bronchioles and thereby keeping them patent, than its effect in opposing lung inflation, which, in fact, exerts a significant effect only late in the inspiratory cycle.

The pressure required to maintain air flow through constricted bronchi is increased in rapid breathing and coughing. The resulting check-valve mechanism operates to trap the inspired air in expiration. The alveoli surrounding the respiratory bronchioles develop a pressure sufficiently higher than the intrabronchial pressure to result in bronchiolar collapse.[6-8] Fry and his co-workers[5] have expressed the situation by stating that cessation of expiratory air flow takes place when the pulmonary pressure is greater than the drop in pressure between the alveoli and the cartilage-supported ends of the larger bronchi. Spirometric tracings have demonstrated the trapping of air produced by the delayed flow of air from alveoli through constricted bronchi, with a resultant progressive increase in the volume of the surrounding alveoli. The check-valve mechanism due to bronchospasm, inflammatory or fibrous tissue, thickening of the bronchioles, and the presence of mucoid secretions is enhanced by loss of the elastic outward traction on the walls of the smaller bronchi.

The net consequence of these factors is a retarded air flow in expiration, which, when aggravated by an augmentation of the pulmonary ventilation, is characterized by an increased turbulent viscosity, the main cause of resistance to air flow. Comparative responses to inhalation of lighter and heavier than air gas mixtures has apparently revealed that the resistance to air flow is higher with increase in the density of the gas breathed, and that the factor of lung tissue viscance, that is, a restrictive effect on air flow produced by change in the contour of the lung, was negligible.[5] Some of the theoretical assumptions of Fry and his group have been disputed.[9] A further qualification might be inserted that in the artificial production of high flow rates, such as in exsufflation with negative pressure, the swiftly induced elevation of the diaphragm of 6 cm., abrupt contraction of lung volume, and shortening of the entire bronchial tree may introduce tissue viscosity as a factor. The high expiratory flow rates produced in this manner would also enhance the factor of turbulent viscosity, especially in the later stage of lung deflation.

With progressive alveolar overdistention as a result of the factors mentioned, that is, diminished lung traction on the alveolar walls and retarded expiratory air flow, lung volume is increased, and the diaphragm is lowered and loses its convex shape; the chest is expanded, and the ribs are spread in a more horizontal direction. Pulmonary ventilation is then accomplished with inefficient contraction of the upper intercostal, the shoulder girdle, and neck muscles.

Symptomatic treatment depends in part on the inhalation of bronchodilator aerosols. The methods of administration have included the hand nebulizer, continuous nebulization with air or oxygen pressure, and more recently intermittent pressure breathing devices which inflate the chest with an inspiratory pressure of 15 to 20 cm. H_2O.[10] However, intermittent pressure breathing requires the simultaneous use of bronchodilator drugs to increase the vital capacity or maximal minute ventilation.[11] Positive (supra-atmospheric) pressure breathing, whether continuous or intermittent, relieves obstructive dyspnea by

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widening the bronchi, and the increasing intrabronchial pressure tends to prevent bronchial collapse.

Intermittent pressure breathing should not, however, be considered a breathing exercise since it does not facilitate training in diaphragmatic excursion. Bullous areas are inflated, as well as other regions of the lungs, and reliance is placed for their deflation on the recoiling pressure of the lungs. Mechanically induced increase in ventilation has been shown to be of value in certain patients with respiratory acidosis. It is not similarly effective in instances where the pH of the blood is normal even though the patient's pCO_2 is high. The accompanying high blood bicarbonate serves to protect the individual against respiratory acidosis, as indicated by Christie[4] and as demonstrated in a series of studies from our clinic in which the homeostatic value of eliminating CO_2 in high concentrations in the expired air has been pointed out.[12] Nevertheless, a recurrent theme is still heard that reducing an elevated blood CO_2 tension is valuable whether or not acidosis is present. The arterial CO_2 content has been observed by a number of investigators to be above 90 volumes per cent,[4,12,13] without irrationality, coma, or any other undesirable mental or physical reaction. In cases in which the blood pH has shifted to indicate an acidosis, hyperventilation by intermittent pressure breathing, including exsufflation with negative pressure, is indicated until, but not after, the pH has become normal. Continued hyperventilation results in progressive loss of base with recurrent episodes of acidosis, as CO_2 fails to be eliminated in the expired air in a concentration imposed by a decrease in arterial pCO_2. A sound therapeutic objective is to employ methods to lower the blood CO_2 by improving the function of the lungs in such a way as to produce better diffusion. These include bronchodilatation, the treatment of infection, and especially the improvement of inefficient breathing patterns.

The disorganized breathing of the patient with pulmonary emphysema is characteristically manifested by an almost exclusively upper thoracic movement in which the alveoli at the periphery and apices are hyperventilated in contrast to those at the hilum which, although more efficient for diffusion, are underventilated.[4] Among the methods available to the patient to improve his respiratory function, the headward tilt of the thorax results in the most striking relief of dyspnea. As the patient lies head down at an angle of sixteen to twenty-two degrees, the institution of diaphragmatic respiration is promptly followed by a consequent improvement in ventilation and perfusion of the lower lobes of the lung. Contraction of the convex dome of the diaphragm, which is placed in the center of the lung and theoretically exerts traction on the hilum, results in a decrease in pulmonary ventilation of 20 to 30 per cent, without lowering of the arterial O_2 concentration or retention of CO_2. In patients with respiratory acidosis, increased elimination of CO_2 is facilitated, with at times a significant increase in the arterial O_2 saturation.[14]

The downward pull of the liver and the spleen on the diaphragm is similarly although not as markedly decreased when the patient sits in a leaning-forward position. The recoiling pressure of the lungs is handicapped by lifting a heavily weighted diaphragm, especially in obese individuals. Patients with pulmonary emphysema suffer from maintenance of the erect posture at considerable cost in

efficiency of ventilatory movement. Had they preserved an inclination to employ all four extremities for purposes of locomotion, this burdensome handicap of the dependent liver and spleen would be avoided since the diaphragm could then move more readily in the horizontal axis.

The decreased minute volume of respiration achieved by use of the diaphragm also effectively lessens the operation of a check-valve mechanism due to retarded air flow and bronchial constriction, especially at the apices and periphery of the lungs. Since any procedure which elevates the diaphragm places it in a more efficient position for subsequent contraction and since the diaphragm itself is not diseased, the use of an "emphysema belt" with pressure applied to the lower abdomen results in the restoration of a negative intrapleural range during inspiration and expiration. In some cases this is followed by clinical improvement. Increasing the intra-abdominal pressure, as by pneumoperitoneum, decreases peripheral venous pressure. This parallels the intrapleural pressure in cases in which diaphragmatic breathing is practiced. In my experience and that of my colleagues, the employment of contraction of the abdominal musculature to facilitate expiratory ascent of the diaphragm does not readily become a spontaneous habit and is not as effective a method of teaching diaphragmatic breathing as that accomplished by the use of the head-down position, the leaning-forward posture, and the application of a specially designed Gordon-Barach belt applied to the abdomen below the umbilicus. Since the training of patients in diaphragmatic respiration was introduced in our clinic eight years ago, 300 patients have been observed in whom moderate to marked symptomatic benefit could be traced to more efficient breathing practices. Although the maximal breathing capacity is not altered, since the test itself results in thoracic breathing, pulmonary ventilation studies reveal a decreased volume of breathing as well as a substantial reduction in the comparative ventilatory response to inhalation of air and 100 per cent oxygen.[15]

A fuller statement of the physiologic and clinical aspects of diaphragmatic breathing and postural exercises is presented elsewhere,[16] but examples of measures employed include manual compression of the lower thorax and upper abdomen three times daily to facilitate emptying of the alveoli and elimination of secretions. Pursed-lip breathing during expiration is a technique in which expiratory air flow is slowed deliberately, a wider diameter of the bronchioles maintained, and undue pulmonary congestion during exercise prevented. Some of these procedures have been patient-inspired as well as patient-applied. The enhancement of diaphragmatic breathing results in increased ventilation of the lower lobes of the lungs and more efficient diffusion of respiratory gases in contrast to intermittent pressure breathing devices that do not selectively aerate the better perfused areas of the lung.

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REFERENCES

1. Hofbauer, L.: Pathologische physiologie der atmung, in Bether, A., Von Bergmann, G., Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen physiologie, Berlin, 1925, Julius Springer.
2. Heckscher, H.: The Emphysema of the Lungs, Its Symptoms and Relations to Other Diseases, Acta med. scandinav. **120**:349, 1945.

3. Becklake, M. R., McGregor, M., Goldman, H. I., and Braudo, J. L.: A Study of the Effects of Physiotherapy in Chronic Hypertrophic Emphysema Using Lung Function Tests, Dis. Chest. **26**:180, 1954.
4. Christie, R. V.: Emphysema of the Lungs, Brit. M. J. **1**:4333, 1944.
5. Fry, D. L., Richard, V. E., Stead, W. W., and Brown, C. C.: The Mechanics of Pulmonary Ventilation in Normal Subjects and in Patients With Pulmonary Emphysema, Am. J. Med. **16**:80, 1954.
6. Neergaard, K., and Wirz, K.: Die messung der strömungswiderstände in den atemwegen des menschen, insbesondere bei asthma und emphysema, Ztschr. f. klin. Med. **105**:51, 1927.
7. Dayman, H. G.: Mechanics of Air Flow in Health and Emphysema, J. Clin. Invest. **30**:1175, 1951.
8. Proctor, D. F., Hardy, J. B., and McLean, R.: Studies on Respiratory Air Flow, Bull. Johns Hopkins Hosp. **87**:225, 1950.
9. McIlroy, M., Selverstone, N., and Mead, J.: Pulmonary Frictional Resistance Measurements With Gases of Various Viscosities and Densities, Fed. Proc. **13**:97, 1954.
10. Gordon, B., Motley, H. L., Theodos, P. A., Lang, L. P., and Tomashefski, J.: Considerations of the Clinical and Physiologic Factors in the Treatment of Chronic Pulmonary Conditions, Dis. Chest. **19**:271, 1951.
11. Fowler, W. S., Helmholtz, F. H., and Miller, R. D.: Treatment of Pulmonary Emphysema With Aerosolized Bronchodilator Drugs and Intermittent Positive-Pressure Breathing, Proc. Staff Meet., Mayo Clin. **29**:7, 1954.
12. Richards, D. W., Jr., and Barach, A. L.: Prolonged Residence in High Oxygen Atmosphere: Effects on Normal Individuals and on Patients With Chronic Cardiac and Pulmonary Insufficiency, Quart. J. Med. **3**:437, 1934.
13. Comroe, J. H.: Problems in Ventilation, Panel Discussion, Anesthesiology **15**:434, 1954.
14. Barach, A. L., and Beck, G. J.: The Ventilatory Effects of the Head-Down Position in Pulmonary Emphysema, Am. J. Med. **26**:55, 1954.
15. Bickerman, H. A., and Barach, A. L.: The Effect of Breathing 100 Per Cent Oxygen in Pulmonary Emphysema: Correlation of Clinical Improvement With Changes in Pulmonary Ventilation, J. CHRON. DIS. **1**:111, 1955.
16. Barach, A. L.: Breathing Exercises in Pulmonary Disease, read at the American Congress of Physical Therapy, Sept. 9, 1954.

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POTENTIALITIES FOR AND LIMITATIONS IN THE CONTROL OF CHRONIC RHEUMATIC FEVER BY PROPHYLACTIC MEASURES

The term "rheumatic state" is deeply rooted in medical parlance to express the peculiar propensity of the rheumatic subject to experience exacerbations and recurrences of rheumatic fever and to indicate the remarkable chronicity of certain manifestations of the disease. The circumstances which predispose to the chronicity of the rheumatic state have yet to be elucidated.

An imposing body of circumstantial evidence has established the group A hemolytic streptococcus as the inciting agent of both initial attacks and recurrences of rheumatic fever. One of the strongest lines of this evidence has been the repeated demonstration during the past fifteen years that recurrences of rheumatic fever can be prevented by protection of the rheumatic subject from infection with group A streptococci.[1] Furthermore, the recent conclusive experiments which indicate that first attacks of rheumatic fever can be prevented by the prompt and adequate treatment of streptococcal pharyngitis[2,3] leave little doubt as to the fundamental etiological role of the group A streptococcus in the initiation of the rheumatic state.

Highly efficient prophylactic measures have been developed which, combined with careful immunologic and bacteriologic studies, should help to determine to what extent control of streptococcal infection in the rheumatic subject will influence the rheumatic state and the natural history of rheumatic heart disease. The administration of monthly intramuscular injections of a long-acting repository penicillin compound, benzathine penicillin (N,N' dibenzylethylenediamine dipenicillin G), provides a means whereby continuous protection against streptococcal infection may be virtually assured the rheumatic subject. A single injection of 1.2 million units provides bactericidal penicillin blood levels against group A streptococci for at least three to four weeks.[4] In the past three years approximately 600 patients who have recently recovered from acute rheumatic fever have received monthly injections of this compound for varying periods of time while on the wards and in the outpatient clinic of Irvington House. No new attacks of rheumatic fever have occurred in this group, and breakthrough of streptococcal infection has been observed rarely during the administration of benzathine penicillin.[5]

Studies of streptococcal antibodies in the sera of patients receiving this form of prophylaxis demonstrate that subclinical streptococcal infection has been prevented. Quantitative immunologic techniques for the measurement of specific antibodies have made possible the detection of streptococcal infection with a high degree of accuracy. Serial determinations of the serum titers of antistreptolysin O, antistreptokinase, and antihyaluronidase have revealed an increase in the concentration of at least one of these specific antibodies in virtually

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all patients infected with group A streptococci.[6] It has been possible to demonstrate evidence of a recent streptococcal infection by this means in almost every patient with acute rheumatic fever when studies are made early in the course of the disease.[7]

When patients with rheumatic fever are protected against new streptococcal infection, the titers of these antibodies fall progressively to average "normal" levels within six months to one year after the onset of the original or current rheumatic attack. This is similarly the case when the disease enters a chronic phase.[8] It has not been possible so far to relate the chronicity of a given rheumatic attack to any particular variation in the behavior of the immune response to streptococcal infection. Serial determinations of these antibodies have been quite useful, however, in revealing whether perpetuation, exacerbation, or reactivation of the rheumatic process is associated with new streptococcal infection.

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In a recent study,[8] 580 patients were observed at Irvington House during recovery from an attack of rheumatic fever. Some of these patients received monthly injections of benzathine penicillin, others received daily oral doses of sulfadiazine or penicillin, and still others received no prophylactic measures. To detect evidence of new streptococcal infection during the period of observation, throat cultures were made at regular intervals, and serum titers of antistreptolysin O, antistreptokinase, and antihyaluronidase were determined serially. After the acute rheumatic process had appeared to have subsided completely for a period of at least two months, no new attacks of rheumatic fever were observed in the absence of bacteriologic and immunologic evidence of new streptococcal infection. New streptococcal infection was demonstrable in all seventeen patients in whom rheumatic recurrences occurred more than two months after clinical and laboratory evidence of the preceding attack had disappeared. These patients had not received continuous chemoprophylaxis with benzathine penicillin. It would appear from these and other studies that acute rheumatic fever, once completely healed, should rarely exacerbate if subsequent streptococcal infection can be prevented.

It may be appropriate at the present time to temper enthusiasm for the potentialities of rheumatic fever prophylaxis. This opinion is in recognition of many of the puzzling features of the rheumatic process that as yet do not appear to be related in any apparent fashion to the antecedent streptococcal infection. The following discussion emphasizes these features.

Susceptibility to Recurrences of Rheumatic Fever.—The attack rate of rheumatic fever following streptococcal epidemics in the general population is approximately 3 per cent.[9] The incidence of rheumatic recurrences following streptococcal infection among patients recently recovered from a rheumatic episode is as high as 50 per cent.[10] The incidence of recurrences of rheumatic fever in the unprotected rheumatic subject is highest in the first few years following a rheumatic attack and thereafter falls off sharply. It will be of considerable importance for future studies to determine whether the high attack rate of rheumatic recurrences in the rheumatic subject is an acquired characteristic which may be eventually lost after several years of continuous antistreptococcal prophylaxis. If the "rheumatic state," as the term applies to

this susceptibility, is actually transitory, some better definition may be possible of the duration for which antistreptococcal prophylaxis must be maintained in the rheumatic subject.

The Delayed Appearance of Rheumatic Heart Disease.—In an era before the widespread use of antibiotics, patients who recovered from a bout of rheumatic fever without apparent damage to the heart frequently developed rheumatic heart disease many years later, often without known new attacks of rheumatic fever.[11] The implication of this observation is either that subclinical valvular sclerosis progresses inexorably following an initial rheumatic attack or that the late appearance of rheumatic cardiac lesions is the result of repeated attacks of rheumatic fever, often subclinical, and caused by intercurrent streptococcal infection. Careful prophylaxis maintained over a period of years, and detailed immunologic studies to detect subclinical streptococcal infection, should determine to what extent the delayed appearance of rheumatic heart disease can be prevented.

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Some light has been thrown on this problem by a recent study[5] of seventy-one patients who had recovered from an attack of acute rheumatic fever without overt stigmas of rheumatic heart disease and who have been followed for a period of three years while receiving monthly injections of 1.2 million units of benzathine penicillin. No evidence of streptococcal infection has been observed in this group during the period of study. Rheumatic cardiac lesions have not yet appeared in any patient.

In the same study, seventy-four patients who had persistent rheumatic cardiac lesions following the subsidence of a rheumatic attack have been maintained on the same prophylactic regimen. Eight were reclassified as having "no heart disease" by the end of the period of observation when organic heart murmurs had disappeared and heart size had returned to normal. Five other patients showed obvious improvement. There was definite progression of rheumatic heart disease in three patients (one of these had severe aortic insufficiency and showed progressive left ventricular enlargement). Therefore only two of 145 rheumatic patients receiving continuous chemoprophylaxis have shown evidence of progressive rheumatic cardiac lesions which might be attributed to persistence of the chronic rheumatic process.

It is conceivable that the prognosis for the young rheumatic cardiac might be improved by continuous chemoprophylaxis. Indeed, the consequences of recurrences in this particular group are often grave. The longevity of the rheumatic cardiac may depend to a considerable extent upon his protection from renewed bouts of rheumatic carditis.

Chronic Rheumatic Fever.—Unfortunately, there is as yet no known way to terminate those attacks of rheumatic fever which enter a chronic phase and result in severe, progressive cardiac damage despite careful protection of the patient from intercurrent streptococcal infection. Actually, the percentage of patients with rheumatic fever in whom the disease assumes a chronic course is relatively small. For example, of 580 patients studied at Irvington House during the past three years only twenty-five (4.3 per cent) showed persistence of clinically apparent rheumatic activity for periods longer than six months.

In a few patients clinical manifestations of active rheumatic fever persisted for at least twenty-eight months despite the prevention of new streptococcal infection.[8]

These severe cases tend to dominate the clinician's impression of the nature of rheumatic fever and to foster a somewhat more gloomy outlook upon the value of antistreptococcal prophylaxis than may be warranted. It is of some interest that in this study, the large majority of patients with chronic rheumatic fever had suffered repeated new attacks before the disease entered a chronic phase. In most patients who suffered unusually protracted bouts of rheumatic fever and who had advanced rheumatic valvular disease, the attack eventually terminated. All signs of rheumatic activity disappeared, considerable cardiac reserve was regained, and new rheumatic exacerbations did not recur during maintenance of continuous prophylaxis for a follow-up period of at least two years. However, it cannot be denied that these patients sustained serious permanent cardiac damage during the chronic stage of the disease which will ultimately result in disability due to the mechanical handicap of deformed valves. Although chronic rheumatic fever remains the most challenging limitation to the value of antistreptococcal prophylaxis, there is little doubt that prevention of the superimposed insult of additional streptococcal infection improves the patient's opportunity for eventual survival and healing.

Histologic Evidence of Myocardial Lesions in the "Inactive" Rheumatic Cardiac.—The finding of Aschoff nodules in the myocardium of the biopsied auricular appendage in a relatively high percentage of patients who have undergone mitral commissurotomy for mitral stenosis has been cited as evidence of the intractable chronicity of the rheumatic process.[12] These lesions frequently bear little relationship to the usual clinical and laboratory criteria for rheumatic activity. They often occur when evidence of recent rheumatic fever is absent. Their relationship to antecedent streptococcal infection has not been clearly defined. In one reported series, the antistreptolysin O titer was low prior to commissurotomy.[13] More detailed immunologic studies are now in progress which should define this relationship more clearly.

The persistence of Aschoff bodies without clinical evidence of rheumatic activity might argue in favor of the concept that rheumatic heart disease progresses at a subclinical level, independent of recurrent rheumatic insults initiated by repeated streptococcal infection. The actual significance of these lesions, however, is still obscure. There is no evidence that patients in whom Aschoff lesions have been found constitute a more serious operative risk than others in whom they have been absent. There has been no correlation of such lesions with subsequent development of the "postcommissurotomy syndrome" or any other untoward postoperative complication which might be anticipated in patients with clinically active rheumatic carditis. In fact, the incidence of these lesions correlates mainly with age (decreasing in frequency sharply in the older age group) and with cardiac rhythm (uncommon in the presence of auricular fibrillation).[13] It is probable that they represent the lingering traces of the healing of a very chronic inflammatory process.

Undoubtedly, some patients with chronic rheumatic carditis will progress to the stage of severe valvular stenosis or insufficiency despite the best current prophylactic measures. There is promise, however, that this eventuality may be averted in the great majority of patients who now recover from an initial episode of acute rheumatic fever with little or no evidence of cardiac damage if subsequent rheumatic attacks are prevented.

The Postcommissurotomy Syndrome.—Of considerable theoretical interest is the delayed appearance, following mitral commissurotomy, of a syndrome of chest pain and fever which in some ways suggests reactivation of rheumatic fever.[14] Again, the absence of antecedent streptococcal infection has not been well documented in the cases so far reported. It is probable, however, from preliminary data,[14] that the postcommissurotomy syndrome is unrelated to recent streptococcal infection. In fact, it appears also to be unrelated to many other factors which would be expected to correlate with the persistence of the chronic rheumatic state, such as the presence of Aschoff lesions in the myocardium, the interval since the last rheumatic episode, or the patient's age.

If it is assumed that this syndrome represents reactivation of rheumatic fever (and this assumption is not yet justified), it would indicate that direct surgical trauma to the heart can exacerbate the rheumatic process. This would imply that the "rheumatic state" persists as a potential specific tissue reaction to injury other than that of streptococcal infection. In my experience, however, there has been no evidence to indicate that trauma is an important factor in producing recurrences of rheumatic fever. In young rheumatic subjects who have received antistreptococcal prophylaxis during the past five years at Irvington House, rheumatic recurrences have not been observed following bone fractures, immunization procedures (with diphtheria and tetanus toxoid), intravenous injections of typhoid vaccine, a wide variety of acute infectious diseases, and indeed anything but a new group A streptococcal infection.

Sydenham's Chorea and Erythema Marginatum.—Finally, a particularly perplexing example of the chronicity of the rheumatic state is the occasional appearance of either Sydenham's chorea or erythema marginatum as an isolated manifestation of rheumatic fever as long as six to nine months after the apparent complete subsidence of a rheumatic attack and without evidence of intercurrent streptococcal infection.[15] When chorea or erythema marginatum appears in this fashion, it is not usually associated with fever, elevation of the sedimentation rate, the presence of C-reactive protein in the blood, or any other manifestation of rheumatic fever.[16]

In our experience nine months has been the longest streptococcus-free interval observed between an attack of rheumatic fever and the delayed appearance of chorea. Beyond this period, Sydenham's chorea has not appeared in a large group of patients who have been maintained on careful prophylaxis. These findings suggest that chorea may be related to antecedent streptococcal infection, often making its appearance much later than other rheumatic manifestations.

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The illustrations of the chronicity of the rheumatic state which have been cited emphasize our ignorance of the pathogenesis of rheumatic fever and the nature of rheumatic inflammation. The hard-won knowledge of the fundamental relationship of the group A streptococcus to the initiation of the rheumatic state, and the effective use of antibiotics for the treatment and prevention of streptococcal infection, offer an approach which may influence profoundly the incidence, morbidity, and mortality of rheumatic fever in spite of the primitive state of our current concepts. The empirical answer to several of the questions raised concerning the relationship of streptococcal infection to the rheumatic state may be forthcoming in the near future by careful observations made during the prolonged administration of continuous chemoprophylaxis to the rheumatic subject.

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REFERENCES

1. Stollerman, G. H.: The Use of Antibiotics in the Prevention of Rheumatic Fever, Am. J. Med. **17**:757 (Dec.) 1954.
2. Denny, F. W., Wannamaker, L., Brink, W. R., Rammelkamp, C. H., Jr., and Custer, E. A.: Prevention of Rheumatic Fever. Treatment of the Preceding Streptococci Infection, J.A.M.A. **143**:151, 1950.
3. Wannamaker, F., Rammelkamp, C. H., Jr., Denny, F. W., Brink, W. P., Houser, H. B., Hahn, E. O., and Dingle, J. H.: Prophylaxis of Acute Rheumatic Fever by Treatment of the Preceding Streptococcal Infection With Various Amounts of Depot Penicillin, Am. J. Med. **10**:673, 1951.
4. Stollerman, G. H., and Rusoff, J. H.: Prophylaxis Against Group A Streptococcal Infections in Rheumatic Fever Patients With New Repository Penicillin, J.A.M.A. **150**: 1571, 1952.
5. Stollerman, G. H., Rusoff, J. H., and Hirschfeld, I.: Prophylaxis Against Group A Streptococcal Infection in Rheumatic Fever Patients by the Use of Single Monthly Injections of Benzathine Penicillin, presented at the Scientific Session of the 18th Annual Meeting of the American Rheumatism Association, San Francisco, June 19, 1954.
6. McCarty, M.: The Immune Response in Rheumatic Fever, in Thomas, L., editor: Rheumatic Fever, Minneapolis, 1952, University of Minnesota Press.
7. Stetson, C. A., Jr.: The Relation of Antibody Response to Rheumatic Fever, in McCarty, M., editor: Streptococcal Infections, New York, 1954, Columbia University Press.
8. Stollerman, G. H., Lewis, A., Schultz, I., and Taranta, A.: The Relationship of the Immune Response to Group A Streptococci to the Course of Acute, Chronic and Recurrent Rheumatic Fever, read before the Second World Congress of Cardiology and 27th Scientific Session of the American Heart Association, Washington, D. C., Sept. 15, 1954.
9. Rammelkamp, C. H., Jr., Denny, F. W., and Wannamaker, L. W.: Studies on the Epidemiology of Rheumatic Fever in the Armed Services, in Thomas, L., editor: Rheumatic Fever, Minneapolis, 1952, University of Minnesota Press.
10. Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three Year Study, J. Clin. Invest. **20**:273, 1941.
11. Bland, E. F., and Jones, T. D.: Rheumatic Fever and Rheumatic Heart Disease; a Twenty Year Report on 1000 Patients Followed Since Childhood, Circulation **4**:836, 1951.
12. Kuschner, M., Ferrer, M. I., Harvey, R. M., and Wylie, R. H.: Rheumatic Carditis in Surgically Removed Auricular Appendages, Am. Heart J. **43**:286, 1952.
13. McNeely, W. F., Ellis, L. B., and Harken, D. E.: Rheumatic "Activity" as Judged by the Presence of Aschoff Bodies in Auricular Appendages of Patients With Mitral Stenosis. II. Clinical Aspects, Circulation **8**:337, 1953.
14. Soloff, L. A., Zatuchni, J., Janton, O. H., O'Neill, J. E., and Glover, R. P.: Reactivation of Rheumatic Fever Following Mitral Commissurotomy, Circulation **8**:481, 1953.
15. Taranta, A., and Stollerman, G. H.: Unpublished data.
16. Stollerman, G. H., Glick, S., Patel, D. J., Hirschfeld, I., and Rusoff, J. H.: Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever, Am. J. Med. **15**:645, 1953.

ECONOMIC VALUES OF REHABILITATION

It is generally agreed that there are approximately 2,000,000 physically handicapped men and women in the United States who, if provided with adequate vocational rehabilitation services, could become employable. It is further estimated that their ranks are increased each year by 250,000 newly disabled persons.

Chronic disease accounts for 88 per cent of this disability, far outranking occupational accidents, which account for 5 per cent; home, highway, and other accidents, another 5 per cent; and congenital conditions, the remaining 2 per cent.

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The economic value to providing essential services to those physically handicapped persons who are feasible of rehabilitation to the extent of employment has been amply demonstrated. In 1952, 64,000 such persons who were rehabilitated through the Federal-state vocational rehabilitation programs added 12,500,000 man-days annually to our national productivity, and their earnings the following year added $115,000,000 in income to our national economic wealth. It is of particular significance that in one year this group of rehabilitated workers will pay $10,400,000 in Federal income taxes alone, thus repaying within three years the total amount invested by the Federal government in their rehabilitation. In addition, they will pay substantial amounts in state and local taxes.

It is of additional significance that a great many of these persons were on public assistance rolls prior to their rehabilitation. In a study of 66,000 persons rehabilitated to employment under the Federal-state vocational rehabilitation program in 1951, 8,000 were found to have been on public assistance prior to their rehabilitation, at a cost of $5,700,000 annually in assistance payments. Their rehabilitation, which cost $4,000,000, was less than three-fourths of the amount it had cost to maintain them on public assistance for a single year. This same group of persons now, however, are earning at the rate of $14,000,000 a year, and instead of being "tax consumers" have become "taxpayers."

In addition to these persons restored to employment under the Federal-state vocational rehabilitation, there are thousands of other physically handicapped persons who are given such opportunities by other public programs, hospitals, medical centers, and various voluntary organizations.

This year, the Office of Vocational Rehabilitation and its state counterparts are embarking on an ambitious program recommended by President Eisenhower, and unanimously passed by both houses of the Congress, aimed at increasing the number of persons rehabilitated each year under the public program from the current 60,000 to 200,000 by 1959. Concurrent with an increase in their direct services are programs for increasing the number of trained rehabilitation workers and rehabilitation facilities, thereby increasing services for all handicapped persons.

Some isolated reports have shown the economic wisdom of providing rehabilitation services for those persons whom age, severity of disability, or other factors prevent from returning to employment. Because of the variety of resources caring for such persons, either in institutions or in their own homes, there are no reliable estimates on the size of this problem nationally or what might be achieved economically if rehabilitation services could be brought to them on a broad scale. This is, and will remain, an academic question until our supply of trained rehabilitation workers is sufficient to permit a sizable expansion of such services.

From our experience to date, however, two facts stand out clearly:

1. Although the pathology of many chronic diseases which cause disability is still irreversible, the economic, social, and emotional sequels need not be.

2. Encouraging as is the new expansion of services for those physically handicapped persons feasible of rehabilitation to employment, we need to balance our thinking and our planning by remembering the needs of those disabled persons who have not yet been reduced to dependency on public aid. To ignore them is to guarantee a continued flow of disabled persons to welfare rolls.

There are no unilateral approaches to these problems. Part of the answer must come from the laboratories as we learn more and more about the processes of the chronic diseases. Another equally important part, however, is the development of increased understanding of the possibilities of rehabilitation for this group and better planning for bringing rehabilitation services to them.

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CRITERIA FOR THE DESIGN OF RESEARCH STUDIES ON CHRONIC DISEASE

The effectiveness of any research must be judged by the generalizations to be drawn from the study. This means that the investigators must have specific knowledge not only of the validity of measurements and observations, but also of their limitations. Laboratory research, especially in the physical sciences, has developed specific techniques and methods for testing the validity and reliability of the observations made. This is due in part to the recognition, through past experience, of the factors that may influence measurements. Thus, no physicist makes measurements of the influence of pressure on the volume of a gas without controlling, or measuring, the temperature. In the biologic sciences we cannot specify, let alone measure, all the factors that may influence specific observations. The device which biologists must use to circumvent their lack of detailed knowledge is the study of many animals in the hope that unknown factors contributing to the measurements will be randomly distributed. In the social sciences, the difficulties are even greater. There are, however, a number of general principles, drawn from laboratory research, which can be usefully applied to investigations in the field of chronic disease. These principles may be expressed in the form of three major questions to be addressed to each study plan.

1. *Is the goal of the study specific and clearly identified?* Essentially, research seeks to answer a question by means of qualitative or quantitative observations and to evaluate the limitations of the generalization obtained. The usefulness of the apparent results will depend on the effectiveness of the research design. The design of a study can be made only in terms of the questions asked. The more specific the question, the more precisely the research can be designed to permit a clear-cut answer. If the questions are broad, diffuse, and poorly defined, so too is the design of the experiment, which will permit only ambiguous answers.

In addition, there must be a precise definition of terms. For example, an investigation of "the prevalence of chronic disease" is meaningless without some explicit definition of both "prevalence" and "chronic disease."

One of the greatest hazards of biologic research is the attempt to answer too many questions at one time, or to answer a complex question by a single experiment. It is better to reduce complex questions to simpler components for which specific answers can be obtained, than to spend time and effort on too complex questions; all too often, in the latter case, the result is failure to answer clearly any part of the question.

2. *Is the experimental design appropriate to answer the questions posed?* This query has many ramifications, but is concerned primarily with determination

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of the duration of the experiment, the choice of the people to be studied and their characteristics, the validity of the observations to be made, the necessity for controls, their adequacy, and the possibility of statistical analysis of the data.

The duration of the experiment is determined by the nature of the problem. Although availability of personnel and facilities may place practical limitations on the duration of a study, first consideration should be given to the scientific requirements. The problem of determining how long a study should be continued is of particular importance in evaluating the effectiveness of programs and treatments in the field of chronic disease. If longitudinal studies are to be used, as they must be for some questions, the problem of sample selection is paramount, since the investigator has a bitter choice to make: a random sample to be heavily decimated with the passage of time, or a selected relatively stable sample.

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The population group to be studied requires careful planning in terms of the questions asked. In survey studies, this must obviously be representative of the entire group from which it derives. Since it is usually impossible to study complete populations, some sampling techniques must be utilized. Consideration must be given to such possible effects on the measurements to be made as economic status, national background, occupation, geographic distribution, or climate. The sample to be studied must be adequate in size. Great advances have been made in the theory and practice of sampling, and competent professional assistance should be sought in designing the selection of subjects.

Other considerations, such as availability for study and cooperativeness, also enter as special considerations, particularly in experiments where repeated observations of the same person are required. In any event, the population studied should be accurately defined in as many ways as possible to permit valid comparisons between different studies.

The observations to be made must first be tested for validity. This requires a clear specification of the goals of the research and the concepts involved. If at all possible, preliminary trials should be made to test objectively the validity of the observations; that is, do the numbers (or observations) recorded offer a true index of the concept being investigated?

While it may not be possible to obtain experimental evidence of validity in many circumstances, one may obtain data on the reliability and reproducibility of observations. This may be done for both quantitative and qualitative data. Observations may be repeated in the same person, or the same information may be acquired in different ways: e.g., the check of patients' statements against previously recorded objective data.

Where questionnaires are used, careful wording is essential. Trial runs with comparable populations should always be made. Ambiguous questions are easily prepared but are fatal in final analysis of the data. Great progress has been made by psychologists in scaling techniques which offer the possibility of a more quantitative evaluation of questionnaire items than can be obtained from item counts alone. These techniques should be carefully considered in planning studies on chronic disease.

Obviously, wherever possible, objective measurements should be utilized. In addition, all questionnaire schedules should be designed with a view to obtaining estimates of amount, degree, or severity. Often graphic rating scales can be adapted to this goal.

Detailed plans for recording and tabulating of all data must be worked out in advance. Where many investigators are involved in a project, it is essential that detailed written instructions giving the objectives of the study, definition of all terms, method of administering tests or questionnaires, items to be covered in an interview, and records to be kept be placed in the hands of each worker. The effectiveness of the instructions, and the usefulness of the record forms, should always be tested in a pilot study.

The time-honored method of using each animal as his own control is of limited use in studies of chronic disease, since the factor of time and increasing age of the subject may introduce changes in the measurements. Consequently, the use of paired groups or individuals is usually required. When individuals or groups are to be matched, the problem of deciding the qualities and characteristics to be matched may become insurmountable, due to lack of knowledge of factors that may influence the measurements being taken. Under such circumstances it may be necessary to use large groups of subjects, selected at random, in the hope that extraneous factors will be equally distributed between the control and experimental groups.

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It is of extreme importance that competent statistical advice be obtained at the original planning of the study. All details of statistical analysis of the data, including tests of reliability and significance, should be laid out in advance. Each item or test to be used in the study must be justified on the basis of its contribution to the plan of the study, and ability to deal with the observation statistically. Many times, efficient planning will permit tests of internal consistency within a body of data which may not be possible after the data are assembled. No tests should be included with the fond hope that the data can somehow be analyzed after they are collected. Such hopes are seldom realized.

3. *Is the proposed study feasible with the personnel and facilities available?* This administrative question should not be confused with adequacy of design. Although compromises can often be made with only a small change in precision of the end result of an experiment, compromises for the sake of expediency should be carefully examined. Part of the planning of research is a realistic estimate of personnel and financial requirements. All too often, no account is taken of time and costs essential to statistical analysis, interpretation of data, and preparation of final reports, to say nothing of costs of publication. All are essential. Unless there is assurance of adequate support for the completion of a study, it is unwise to start it. It is better to simplify the questions and reduce the magnitude of the problem than to attempt too much. A specific answer to a smaller question is more desirable than an indefinite or erroneous answer to a broad diffuse question, no matter how important the latter may be.

N. W. Shock

Book Reviews

A MANUAL FOR CLINICAL ALLERGY. By John M. Sheldon, M.D., Robert G. Lovell, M.D., and Kenneth P. Mathews, M.D. Philadelphia and London, 1953, W. B. Saunders Company.

The authors, all associated with the University of Michigan School of Medicine, have prepared this manual for those physicians "interested in devoting" part of their time in allergy or "in establishing an allergy practice." It is not a textbook in the ordinary sense and devotes less space to theoretical and ultrascientific discussions. With sufficient outline of terminology, the manual starts at once on the practical aspects of evaluating the allergic patient. The authors draw liberally from their own experience with regard to important techniques and pitfalls in history-taking and laboratory procedures. A list of twenty tests of varying types are outlined in method and their value tersely summarized—not all of which the reviewer thinks will be practical for many of the readers. The staining methods for nasal secretions are given in detail.

Skin tests are given a full discussion, as to both their nature and reliability. Too frequently a manual such as this glosses over the interpretation significance. While these authors suggest rather extensive lists of foods, inhalants, and pollens to be used in testing, they are careful regarding "face-value" interpretation of either positive or negative reactions. The reviewer shares the authors' views restricting the use of intracutaneous, passive transfer, and ophthalmic tests.

A very good discussion of hyposensitization as treatment, together with directions and suggestions, is followed by a chapter on constitutional reactions. The proper use of antihistaminics and cortisone is described—both for serum sickness and for status asthmaticus. Aerosol therapy is given a short but adequate appraisal and description.

The chapter on useful drugs in allergic diseases is perhaps more detailed than would be expected in most manuals, but there is no doubt in the reviewer's mind that such a classification-description and appraisal is extremely valuable. Since this is followed by a chapter on "Drug Allergy," the reader will have a sound basis for his selection and use of palliative drug therapy.

Chapter 10, on food allergy, is very comprehensive and includes not only the role of history and tests but also gives samples of elimination diets and special recipes to be used in substitution menus. The authors devote a special chapter (12) to the patch test. This might well have been included earlier in the manual when other types of laboratory and testing techniques were presented. Pediatricians may be disappointed in the short discussion of atopic eczema and the role of secondary infection.

The discussion of aero-allergens is most valuable and most inclusive. Excellent plates enable those who are interested to identify the common plants and their offending pollens. While it is doubtful if the average practitioner will make local pollen, fungus, or mold surveys, he will understand the role they play by having read this manual.

Endocrine aspects of allergy, vascular allergy, and psychologic factors compose three short final chapters of the manual proper. Enthusiasts for these newer considerations may be disappointed with this brevity of attention, but in writing a manual rather than a textbook, the authors have thereby avoided overweighing these less-explored or less-exact aspects of allergy.

Chapters appended to the main manual offer plans for efficient handling of patients and materials, and preparation of extracts for testing and bacterial vaccines for inoculation.

With increasing recognition and incidence of allergic diseases, the manual is very timely, very complete. As a field of clinical medicine, allergy is, of course, far from an exact scientific basis for diagnosis and treatment. But with our present concepts and terminologies, the authors have done a fine service in offering a practical approach both for understanding and for care of the allergic patient. The manual should prove helpful to both specialist and general practitioner.

Francis Scott Smyth

CARDIOVASCULAR SURGERY. By Gerald H. Pratt, M.D., Associate Clinical Professor of Surgery, New York University College of Medicine. Pp. 843, with 358 illustrations on 261 figures and 4 plates in color; indexed. Philadelphia, 1954, Lea & Febiger. Price $15.00.

The pressing need for a good text on cardiovascular surgery will probably elicit a number of books in the near future. Pratt's *Cardiovascular Surgery* is one of the first to appear since this field began to broaden strikingly, and is a valuable book in many respects. It covers all branches of cardiovascular surgery and contains a valuable list of references. The section on cardiac surgery, and especially that on congenital defects, is not nearly as accurate nor as complete as the larger portion of the book devoted to peripheral vascular surgery, a field in which the author is an outstanding authority. The portion on peripheral vascular surgery, which in most respects is excellent, is not up to date concerning the direct attack upon arteriosclerotic lesions. Excision and grafting of the aorta for aneurysm, or for thrombotic obliteration, are only briefly mentioned although, in the last several years, this has become one of the fields in peripheral vascular surgery most productive of grateful patients.

The literary style is concise but in some sections choppy. The frequently encountered split infinitive is not nearly so disturbing to this reviewer as the author's use of the patient as the object of the verb "to operate" without the preposition "upon." This not infrequent corruption of the idiom elicits visions of handling the patient like a crane or streetcar.

It is probable that the book will see another edition in which these and other minor errors can be corrected.

Henry T. Bahnson

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THE TREATMENT OF THE ALCOHOLIC. By Fritz Kant, M.D., Professor of Neuropsychiatry, University of Wisconsin Medical School. Pp. 130; indexed. Springfield, 1954, Charles C Thomas, Publisher. Price $4.75.

This newest book on "the treatment of the alcoholic" is simply and straightforwardly written and derives from its manner of presentation both its merits and its limitations. Seemingly addressed primarily to the general medical and even the interested lay audience (it has in the back a glossary of the medical terms used in it with simple, nontechnical definitions), it states clearly a number of basic propositions relevant to a therapeutic outlook on the problem of alcoholism. One is that the alcoholic is sick and needs medical help—that the problem of alcoholism needs conceptualization in medical-therapeutic, rather than in moral-condemnatory, terms. A second is that the explanatory mechanisms of the alcoholic state should be sought in experiential vicissitudes and that a dwelling on a postulated hereditary psychopathic disposition leads practically to a resigned fatalism of outlook. A third is a clear statement of the integration of both Antabuse and condition-reflex treatments as adjunctive to an over-all psychotherapeutic approach. And a fourth is a welcome recognition of the complex role the various family members may play in the equilibrium of the alcoholic patient, with a needed emphasis on a treatment planning that encompasses a working with the problems of the family in regard to the alcoholic member. There are, too, concise and informative discussions (for the educated layman) of the nature of the various alcoholic psychoses and types of organic brain syndromes derivative from alcoholism as well as of distinctions between alcohol intoxication, problem drinking, alcohol addiction, and so forth.

Where the book suffers is in its misleading oversimplification. It begins with a one-page chapter entitled "Why Do People Drink?" and answers its question in the fifth sentence, "Analysis of the alcohol effect on the emotional aspect of the personality gives a *simple* explanation. The world is fundamentally changed . . . that is the reason that people drink." Such simplified formulations appear again in the listing of three major "Abnormal Personality Types Among Alcoholics." It is just these sorts of oversimplified psychologic concepts which lead to the difficulty that the author decries of relatives (and patients) who come stating, "(he) is an alcoholic—

there must be a reason. Find *the* unconscious conflict or *the* traumatic child experience and remove it." One must wonder, too, whether such a simplification of psychodynamics does not engender an unwarranted easy optimism in the treatment of the alcoholic.

The presentation of the positive side of the book's message—that alcoholism can be understood as a psychologic malfunctioning and can be treated by psychotherapy—is to this reviewer the most confused part of the whole contribution. There is an emphasis on "deep psychotherapy" which has to do with an "attack (on) the sources of feelings of guilt, insecurity and inferiority" combined somehow with "the role of religious conversion as a healing factor" since "a strong, concrete faith and neurosis do not occur together." Additionally, the nature and the treatment of alcoholism are stated to be *essentially* different from the nature and the treatment of the neuroses since "a neurosis can be cured in a psychological sense (alone) and alcoholism cannot." In the alcoholic, "habit formation and social pressure" that would lead to attempts at renewed drinking even after cure must likewise be combatted and uprooted. In this, of course, is represented the still unsolved problem that psychotherapeutic methods of whatever depth or duration have still not led to cure in the sense of enabling the exalcoholic to become a normal, social drinker. However, the whole presentation of the immense psychotherapeutic problems that do exist tends to confuse rather than clarify the psychodynamic issues involved. This is especially unfortunate in a book apparently aimed for wide dissemination to the nonspecialist audience.

Robert S. Wallerstein

RESERPINE (SERPASIL) AND OTHER ALKALOIDS OF *RAUWOLFIA SERPENTINA*: CHEMISTRY, PHARMACOLOGY, AND CLINICAL APPLICATIONS. By Frederick F. Yonkman and Frank L. Mohr (Conference Chairman), and others. Annals of the New York Academy of Sciences. Vol. 59, Art. 1. Pp. 140. Edited by Roy Waldo Miner. New York, 1954, New York Academy of Sciences.

This series of papers, which was presented at a conference held by the New York Academy of Sciences, recounts the fascinating story of the rediscovery of the pharmacologic and clinical effects of the alkaloids of *Rauwolfia serpentina*. This plant, which grows in India and adjacent countries and bears the name of Leonard Rauwolf, a sixteenth century German physician and botanist, had been used for hundreds of years in India and Europe in the treatment of insomnia, hypochondria, and anxiety states. In 1931 Indian chemists isolated the first of a series of crystalline alkaloids from it, and in 1933 the hypotensive activity of extracts and root preparations was described in India. Since that time there has been steadily increasing interest in the properties of extracts of *Rauwolfia serpentina* and of its active alkaloid, reserpine, and in the use of these preparations as adjuncts in the management of hypertension and of anxiety states. There is general agreement that Rauwolfia (and reserpine) are hypotensive agents of modest potency with bradycrotic and sedative action, most effective in relatively young patients with labile hypertension, and useful in patients with more fixed hypertension when given in combination with the more potent hypotensive drugs, such as hydrazinophthalazine, hexamethonium, pentapyrrolidinium, and veratrum. Rauwolfia and reserpine appear to reduce vasoconstrictor tone by central action, presumably on sympathetic vasoconstrictor centers in or near the hypothalamus. The sedative effects of Rauwolfia and reserpine have proved to be useful not only in patients with hypertension, but also in the management of some psychoneurotic patients, in whom these drugs have been observed to reduce anxiety, obsessive-compulsive drives, and excessive inhibition and reticence. Their reported usefulness in some schizophrenic patients does not yet appear to have been substantiated. The story of the rediscovery of the pharmacologic and clinical effects of *Rauwolfia serpentina* alkaloids, as recounted in this series of papers, makes interesting and rewarding reading.

David Grob

THE PATHOLOGY OF TRAUMA. By Alan Richards Moritz, M.D., Professor of Pathology and Director of the Institute of Pathology, School of Medicine Western Reserve University. Ed. 2. Pp. 414, with 126 illustrations; indexed. Philadelphia, 1954, Lea & Febiger. Price $8.50.

The new edition of *The Pathology of Trauma*, with the many revisions and considerable increase in size over the first, establishes it as the best available reference source on the subject. It is divided into eleven chapters covering the General Pathologic Effects of Trauma, Trauma and Infection, Trauma and Tumors, individual chapters for the injuries of the various anatomic systems within the body, and finally, one on Medicolegal Autopsy. There are extensive revisions over the first edition with some of the outstanding improvements being a discussion of the role of ACTH and the adrenal cortex in the response to trauma, new illustrations of gunshot wounds, a more complete discussion of infection and trauma with sections on scratch wounds and injuries from lower animals and insects.

The section on cardiac injury resulting from excessive physical exertion and the discussion of the relationship of sudden cardiac death to occupational stress are most lucid presentations of the medicolegal aspects of a problem which is the source of an enormous amount of litigation today. The expert witness as well as the trial lawyer in compensation work would do well to familiarize himself with this.

The section on mechanical injury of the central nervous system has been extensively revised by this reviewer.

In the chapter on the medicolegal autopsy, there are remarks about identification by recognition as well as skeletal remains, a discussion of the sequence of post-mortem changes and their medicolegal significance including entomologic and botanical sources of evidence and a description of the essential components of the medicolegal autopsy record.

The concise presentation of so much information of importance to the clinician and the surgeon dealing with traumatic cases as well as to pathologists and lawyers makes it an extremely useful book and assures its favorable acceptance by all who have interest in the relationship of injury and disease.

Russell S. Fisher

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